EVALUATION OF BRAINSTEM AUDITORY EVOKED POTENTIAL AND SERUM ZINC LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

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CERTIFICATE

This is to certify that the dissertation entitled **"EVALUATION OF BRAINSTEM AUDITORY EVOKED POTENTIAL AND SERUM ZINC LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER"** by Dr.J. Anitha Ponmalar for M.D Physiology is a bonafide record of the research done by her during the period of study (2012-2015) in the Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai – 600 003.

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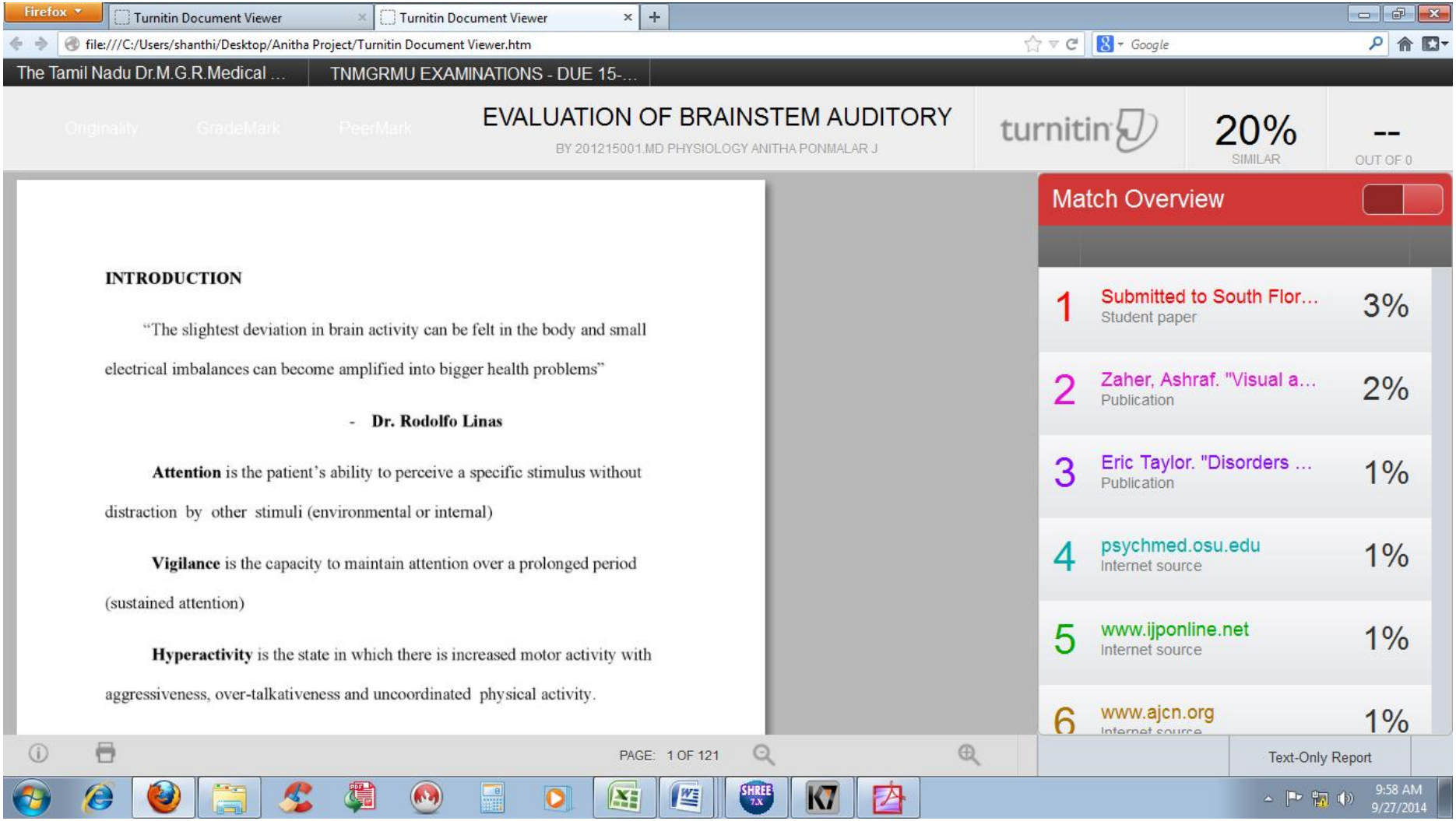
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INTRODUCTION
"The slightest deviation in brain activity can be felt in the body and small electrical imbalances can become amplified into bigger health problems"
- Dr. Rodolfo Linas
Attention is the patient's ability to perceive a specific stimulus without distraction by other stimuli (environmental or internal)
Vigilance is the capacity to maintain attention over a prolonged period (sustained attention)
Hyperactivity is the state in which there is increased motor activity with aggressiveness, over-talkativeness and uncoordinated physical activity.
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ABBREVIATIONS

ADHD	-	Attention Deficit Hyperactivity Disorder
ADD	-	Attention Deficit Disorder
ABR	-	Auditory Brainstem Response
BAEP	-	Brainstem Auditory Evoked Potential
BERA	-	Brainstem Evoked Response Audiometry
AVCN	-	Anterior Ventral Cochlear Nucleus
SLR	-	Short Latency Response
MLR	-	Middle Latency Response
LLR	-	Late Latency Response
PCVN	-	Posterior Ventral Cochlear Nucleus
DCN	-	Dorsal Cochlear Nucleus
SPL	-	Sound Pressure Level
dB	-	Decibel
IPL	-	Inter Peak Latencies
EEG	-	Electro Encephalography
ERP	-	Event Related Potentials
Hz	-	Hertz
MRI	-	Magnetic Resonance Imaging
PET	-	Positron Emission Tomography
DTI	-	Diffusion Tensor Imaging

ABSTRACT

EVALUATION OF BRAINSTEM AUDITORY EVOKED POTENTIAL AND SERUM ZINC LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

Degree for which submitted	:	Doctor of Medicine(MD) in Physiology
Supervisor and guide	:	Prof. Dr. K. Padma Director and Head of the Department
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Year	:	2014

BACKGROUND

Attention Deficit Hyperactivity Disorder is a behavioural and neurocognitive condition characterized by developmentally inappropriate and impairing levels of gross motor overactivity, inattention and impulsivity. Brainstem Auditory Evoked Potential (BAEP) is an important neurophysiological tool which can be used to assess the functional integrity of the auditory pathway and its neurotransmission. It has been widely used for the detection of asymmetrical conduction of

auditory stimuli in the auditory pathway. Using BAEP, we can easily detect the early changes occurring in the auditory pathway in children with ADHD and detect hearing impairment which may contribute to inattention even before clinical manifestation.

AIM OF THE STUDY

- To determine the functional integrity of auditory pathway in children with ADHD by recording brainstem auditory evoked potential.
- To assess serum zinc levels in these children.
- To find the correlation between serum zinc levels and Brainstem auditory evoked potential in children with ADHD.

MATERIALS AND METHODS

30 boys with ADHD in the age group 6 - 11 years without any clinical evidence of hearing impairment were included in the study. Controls were age and BMI matched healthy children. Both the controls and ADHD children were subjected to BAEP and serum zinc levels were also measured. The data were analyzed by Student ‘t’ test.

RESULTS

ADHD children showed significant prolongation of wave III, V absolute latencies and I-III, I-V IPLs of BAEP. The serum zinc levels were significantly decreased in ADHD children when compared to controls suggesting the contribution of zinc in the pathogenesis of ADHD.

CONCLUSION

There was significant prolongation of central conduction time in ADHD children even though there was no clinical evidence of hearing impairment assessed by pure tone audiogram prior to the study. Hence BAEP can be utilized as an objective electrophysiological tool to evaluate the functional integrity of auditory pathway from the external ear to lower brainstem.

KEY WORDS

Attention Deficit Hyperactivity Disorder, Brainstem auditory evoked potential, Absolute latency, Interpeak latency.

1. INTRODUCTION

"The slightest deviation in brain activity can be felt in the body and small electrical imbalances can become amplified into bigger health problems"

- **Dr. Rodolfo Linas**

Attention is the patient's ability to perceive a specific stimulus without distraction by other stimuli (environmental or internal)

Vigilance is the capacity to maintain attention over a prolonged period (sustained attention)

Hyperactivity is the state in which there is increased motor activity with aggressiveness, over-talkativeness and uncoordinated physical activity.

Impulsivity is defined as failure to ignore appealing stimuli other than target stimuli which leads to loss of sustained attention to a particular target task hindering successful completion of that task.

Attention is maintained **by Ascending Reticular Activating System** and its diffuse efferent projection onto non-specific thalamic

nuclei (intralaminar and midline reticular nuclei) and then to the neocortex especially the prefrontal (dorsolateral frontal cortex area 45 and 46, orbitofrontal cortex area 11 and 47) and anterior cingulate (limbic) cortex corresponding to brodmann area 24, 32 and 33. RAS sends a strong facilitatory drive to the cortical neurons raising their background excitability (EEG activity).

The functional importance of reticular formation remained unrecognized until 1946 when **Magoun and Moruzzi**[103] found that electrical stimulation of ventromedial part of medullary reticular formation caused inhibition of cortically induced and reflexly produced movement. Magoun in 1949 showed that high frequency stimulation of midbrain reticular formation produces EEG alerting response and arouses a sleeping animal. Damage to this area produces a comatose state. Electrical stimulation of posterior hypothalamus also produces arousal. The ascending reticular activating system is responsible for the awake state recorded in EEG.

Jasper and Hambery[66] found that stimulation of non specific projection system of thalamus which consists of midline nuclei, intralaminar nuclei, ventralis anterior nuclei and reticular nuclei resulted

in widespread rhythmic activity and concluded that nonspecific projection system of thalamus is the rostral end of reticular activating system(discovered by Moruzzi and Magoun)

The reticular formation is the phylogenetically old reticular core of the brain which occupies the central portion of medulla and midbrain surrounding the fourth ventricle and cerebral aqueduct. It contains the cell bodies and fibres of aminergic systems such as dopaminergic, nor adrenergic and serotoninergic systems and also cholinergic systems and project to widespread areas of central nervous system where they influence motor functions, consciousness, attention, sleep and wakefulness, motivation, emotion, reward processing and addiction. All systems in reticular formation are influenced by projections from other brain areas and can inturn influence the functions of those areas. Thus reticular formation is **"THE INTEGRATOR IN CENTRAL NERVOUS SYSTEM"**

The brainstem reticular formation comprises of medullary, pontine and midbrain reticular formation. Structurally it is classified into

1. Neuronal aggregates
2. Reticular pathways

a. Afferent connections

b. Efferent connections.

NEURONAL AGGREGATES OF RETICULAR FORMATION

Nuclei of median column:

Lie in the midline and called as raphe nuclei

Nuclei of medial column:

Lie lateral to nuclei of median column and called as magnocellular nuclei as these are made of large cells.

Nuclei of lateral column:

Lie lateral to medial column and called as parvocellular nuclei as these are made of small neurons.

Functional neuronal aggregates:

They are not anatomical entities but have fairly well defined physiological functions. Eg: cardiac, respiratory and vasomotor centres.

Connections of Reticular Formation

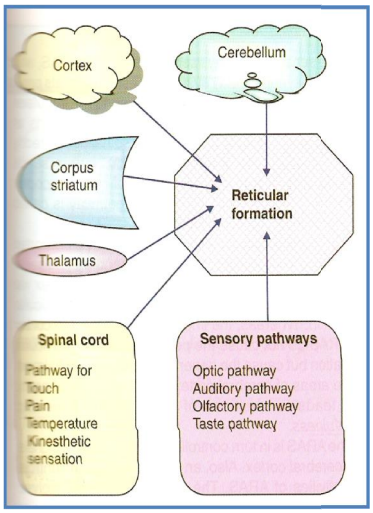


Fig. 1 -Afferent connections of reticular formation

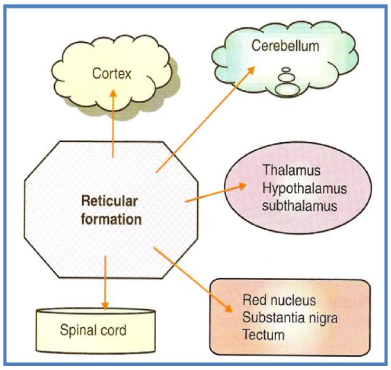


Fig. 2 – Efferent connections of reticular formation

RETICULAR PATHWAYS

Afferent connections:

1. From spinal cord – spinoreticular tract
2. From cranial nerves – brainstem afferent
3. From Tectum(superior and inferior colliculi) – tectoreticular tract
4. From cerebellum – cerebello reticular tract
5. From basal ganglia directly and indirectly

6. Neocortex – corticoreticular fibres from motor and sensory cortex, orbital , prefrontal, parietal and temporal lobes, cingulated gyrus and collaterals from corticofugal fibres.
7. Limbic lobe including amygdala and hippocampus.

Efferent connections:

1. To spinal cord – reticulospinal tract
2. To brainstem – reticulobulbar fibres
3. To cerebellum
4. To red nucleus, substantia nigra and tectum in midbrain
5. To thalamus, subthalamic nuclei and hypothalamus
6. To corpus striatum, neocortex and limbic lobe indirectly through thalamus and hypothalamus.

FUNCTIONS OF RETICLAR FORMATION

1. Through functional neuronal aggregates influences respiratory, circulatory ,gastrointestinal and visceral functions.

2. The descending fibres influence motor control and stretch reflexes, sensory modulation and autonomic activity

3. The ascending fibres which constitutes the ASCENDING RETICULAR ACTIVATING SYSTEM controls the levels of cortical activity(attention, alertness,- wakefulness) and electrical activity of the cortex (EEG)

Reticular Activating System is a complex polysynaptic pathway arising from Brainstem reticular formation which projects to intralaminar and reticular nuclei of thalamus which inturn projects diffusely and non-specifically to wide regions of cortex including frontal, parietal, temporal and occipital cortices.

Collaterals funnel into ARAS not only from long ascending sensory tracts but also from trigeminal, auditory, visual and olfactory systems. The complexity of neuronal network and degree of convergence abolishes modality specificity and most reticular neurons are activated with equal facility by different sensory stimuli.

NEUROTRANSMITTER SYSTEMS OF RAS

Dopaminergic system

Dopaminergic neurons are located in two anatomically and functionally distinct areas namely substantia nigra and ventral tegmental

area. Dopaminergic cell bodies in substantia nigra projects to caudate nucleus and putamen and play a role in the control of movement. The ventral tegmental area in the rostral midbrain has widespread projections to various CNS areas and plays a role in circuitry involved in reward, motivation, emotion, impulse control and decision making.

Nor-adrenergic system:

Neurons using norepinephrine as the principal neurotransmitter are clustered in pons next to fourth ventricle in locus coeruleus and also scattered throughout the lateral tegmentum of brainstem. Activities of these neurons are either tonic (constant and continuous) or phasic(increases periodically and temporarily).The main function of these neurons is to modulate attention, arousal, mood and pain in conjuction with serotoninergic and dopaminergic systems.

Tonic firing of noradrenergic neurons contributes to general levels of arousal and attention whereas phasic firing helps us to focus attention onto a specific task while suppressing distracting stimuli. But too much of activation of noradrenergic neurons decreases our ability to focus on one specific task.

Serotoninergic system:

Located in raphe nuclei which is a collection of neurons in the midline along the entire length of brainstem and spinal cord and modulates regulation of mood, appetite, sleep, state of wakefulness, modulation of pain and some cognitive functions.

Cholinergic system:

Located in the tegmentum of pons and plays a neuromodulatory role by enhancing functioning of synapses. Cholinergic projections to the thalamus strengthens the excitatory glutaminergic output from thalamus to cortex and plays a role in arousal and motor functions.

Histaminergic system:

Located in tegmentum of midbrain and functionally related to cluster of histaminergic neurons located in the posterior hypothalamus. Projections of these neurons play a role in general arousal and alertness.

When activity of noradrenaline and serotonin containing neurons is dominant, there is reduced level of activity in acetylcholine containing neurons in the pontine reticular formation and this activity contributes to

awake state. Phasic bursts of noradrenaline release causes arousal state and focusing of attention.

Thus attention is mediated by a complex interaction of limbic, neocortical and ascending reticular activating systems. Damage to many brain areas can disrupt attention. For eg: metabolic disturbances, drug intoxication, extensive bilateral cortical damage, bilateral lesions of frontal lobe or limbic system.

Attention Deficit Hyperactivity Disorder is the most common neurobehavioral disorder of childhood affecting school aged children characterized by inattention, increased distractibility and difficulty sustaining attention, poor impulse control, decreased self-inhibitory capacity and motor restlessness inappropriate for that particular age **(Durston.S)** [45]. They have poor school performance **(Barkley, RA)**[19] due to difficulty in focusing their attention efficiently and easy distractibility **(Kennemans JJ** [72] **et al) (Vanderstelt O** [163] **et al) (Van Mourik Rooster** [162] **et al)**

In addition to poor school performance, they have problems like interpersonal relationships with family members and peers and also they

have low self esteem. ADHD often co-exists with emotional, behavioral, language and learning disorders.

DSM-IV (4^{th} edition of American Psychiatric Association's Diagnostic and statistical manual) states that the prevalence of ADHD is 5-8% **(Polanczyk G [115] et al)** and identifies three subtypes of ADHD according to **(Chhabildas N[35] et al)** namely

1. Predominantly inattentive type (30%)

2. Hyperactive-impulsive type(9%)

3. Combined type(61%) which is the commonest type**.**

ADHD is 3-4 times more common in males (9.2% in males and 2.9% in females), but the inattentive subtype is more common in females.

There is no single causal factor in the aetiology of ADHD. Genetic and environmental factors acting during foetal and postnatal development such as maternal smoking and toxins such as lead may play a role. It commonly occurs following damage to CNS (prematurity, TBI) ,toxin exposure or as a sequelae of CNS infection. Attention is mediated by multiple neuronal circuits involving many neurotransmitters and so it is difficult to identify the exact deficit in ADHD(**Solomon**

M[138] et al). Morphologic and functional brain dysfunction including moderate reduction in size of dorsolateral prefrontal cortex, corpus callosum, basal ganglia and cerebellum**(Makris N [90] et al)** and hypoperfusion of frontal-striatal dopamine pathways may be implicated**(Sillitoe RV [137] et al)**

Molecular genetic studies reveals strong genetic component such as abnormalities in dopamine transporter gene, norepinephrine transporter gene and choline transporter gene. Patients with predominantly inattentive ADHD had changes in norepinephrine transporter gene , predominantly hyperactive-impulsive type had altered dopamine transporter gene and combined type had altered choline transporter gene. Alterations in Dopamine Transporter Gene (DAT1) and D4 Dopamine Receptor Gene (DRD4) are more likely to have functional significance **(Faraone SV[49] et al).**

Evoked potentials are electrical potentials recorded in response to an external stimulus which may be visual, auditory or somatosensory.

Brainstem Auditory Evoked Potential is produced by presenting auditory stimuli in the form of clicks to the ear which results in sequence of waveforms which are recorded by surface electrodes placed over the

scalp. These waveforms are specific for different structures in the auditory pathway and so provides specific localization of pathology .

Brainstem Auditory Evoked Potentials are markers which provide precise information about the delay in the transmission of auditory impulses from the periphery to the brainstem (**Hood LJ 1998)**[61]. BAEP in the first 10 milliseconds (Early Latency Response) provides information about the functional integrity of the auditory pathway from the vestibulo-cochlear nerve upto midbrain inferior colliculus**.(Jacobson J.T.1985)**[65]

Brainstem Reticular Activating system is responsible for formation of evoked potentials and neurotransmitter imbalance in the fronto-striatal network which is the hallmark of ADHD will lead to changes in the amplitude and latency of waveforms of BAEP. It acts as an important neurophysiological tool for assessing the delay in transmission of auditory impulses and assists in the early diagnosis of ADHD.

Zinc is a cofactor for metabolism of many neurotransmitters and fatty acids. It is necessary for 100 different metalloenzymes and complex metal enzymes **(Arnold LE, Pinkham SM et al)** [13] **(Toren P et al)**[161]. It

also regulates dopamine metabolism which is involved in the pathogenesis of ADHD. Dopamine transporter has an endogenous zinc binding site and zinc acts as a potent non-competitive blocker and prevents dopamine binding to the dopamine transporter and thus increases the extracellular availability of dopamine by decreasing its degradation **(Lepping P. Haber M)**[82]

Published reports of the role of zinc in ADHD shows low levels of zinc in serum, red cells, hair, nails and urine of affected children**(Arnold LE, Di silvestro RA)** [11]. Zinc can be considered as an adjuvant in treating ADHD along with approved pharmacological stimulant therapies **(Akhondzadeh S et al)**[4]**.**

Hence considering these above factors,the present study was undertaken to evaluate the functional integrity of auditory pathway in children with ADHD by performing BAEP and to find out the role of zinc in the pathogenesis of ADHD children by comparing serum zinc levels in normal children and children with ADHD.

Review of Literature

2. REVIEW OF LITERATURE

Attention Deficit Hyperactivity Disorder is a behavioral and neurocognitive condition characterized by developmentally inappropriate and impairing levels of gross motor over activity, inattention and impulsivity **(APA 2000)** which results in deficits of executive functions. It involves impaired ability to plan a work and to execute that plan. The prevalence of ADHD has been increasing in the recent years probably due to formation of nuclear families rather than joint families and also poor parenting techniques.

BAEP is a neurophysiological test which can be used to assess the integrity of auditory pathway and to localize defective neurotransmission in the pathway and can be used to identify hearing impairment in ADHD which may contribute to attention deficit in these children. Only few BAEP studies have been reported in ADHD children and these studies have shown increase in latency of BAEP waves and so with this background , the present study has been taken up to assess the integrity of auditory pathway and its neurotransmission in ADHD children.

As several researches now-a-days point out to nutritional factors influencing mental health, the present study is aimed at measuring serum

zinc levels in children with ADHD to identify if zinc deficiency has played a role in the pathogenesis of ADHD.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Early in the mid-nineteenth century the problems of inattentiveness and overactivity in children were recognized by Heinrich and Hoffman **(struwwel peter [149] et al)** in the moralistic children's book Slovenly Peter which featured the characters Fidgety Phil and Harry. In 1902, ADHD was discovered by George Still **(Still. G[145] et al)** as the behavioral sequelae of viral encephalitis called as Still's disease. He described about the overactivity and impulsivity of these children and he believed to have a combination of organic and environmental factors resulting in lack of inhibitory control(impulsivity) and inattention in these children.

After the influenza pandemic in 1919 to 1920, children who survived developed severe behavioral problems similar to that described in Still's monograph. The flu survivors were thought to have organic brain damage and so the condition was termed as Minimal Brain Damage Syndrome.

In 1937, C.Bradley published a report that d,l-amphetamine reduced restlessness and improved concentration in children with

behavior problems in a residential treatment centre. This concept was ignored for about 30 years when Keith Conners and Leon evaluated the efficacy of d- Amphetamine in a double blind placebo controlled trial for children with learning disability and behavior problems. In the early 1960's the condition was renamed as Minimal Brain Dysfunction which implied specific anatomic location which was not proved till then.

Genesis of the terms ADHD and Hyperkinetic Disorder

Initially **ICD-9** (International Classification of Diseases and Related Health Problems) and **DSM** (Diagnostic and Statistical Manual of Mental Disorders) adopted the same descriptive definition for this condition termed hyperkinetic syndrome of childhood. This term believed that hyperactivity was the core feature of this disease. But further research suggested that the main disability associated with this condition is the difficulty in maintaining sustained attention and impulsivity whereas motor overactivity is only secondary. This resulted in 1980 version of **APA** (American Psychiatric Association) classification which renamed the condition as Attention Deficit Disorder (ADD). This included three symptom categories as diagnostic criteria in which three out of five inattentive symptoms, three out of six impulsive symptoms

and two out of five overactivity symptoms was proposed. Based on this three subtypes of ADD were described namely Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder without Hyperactivity and a Residual type that included adults with ADD symptoms but no longer met childhood ADHD criteria.

In 1987, DSM version named as DSM III-R, which included a single criterion list requiring 8 of the 14 possible symptoms of hyperactivity, impulsivity and inattention was published. Duration criteria was added stating that the behavior should be present since age 7 years and for atleast 6 months. This version had no sub groups.

In 1994, APA published the 4th edition of DSM and in 2000, a Text Revision, DSM IV-TR which is the current version.

Diagnostic Definition of ADHD

There are two main approaches to define disorders of inattentiveness, hyperactivity and impulsiveness namely DSM IV-TR (APA 2000) which recognizes the term "Attention Deficit Hyperactivity Disorder" and ICD-10 (WHO , 1992) which uses the term "Hyperkinetic Disorder". Both are based on the same descriptions of behavior but the items are weighed differently **(swanson, sergeant, Taylor et al)** [150].

Hyperkinetic Disorder (ICD – 10) requires all three components to be present and that the diagnostic criteria must be met in more than one situation(both home and school) and excluded by presence of other disorders such as autism and anxiety states.

ADHD (DSM-IV) is divided into 3 subtypes

1) Combined type

2) Inattentive type

3) Hyperactive/impulsive type

With five main diagnostic criteria

1. Onset before 7 years.

2. Duration greater than 6 months.

3. An 18- item symptom list of which 6 of 9 inattention (or) 6 of 9 hyperactive/impulsive symptoms have persisted for atleast 6 months to a degree that is maladaptive and inconsistent with developmental level.

4. Some impairment in two (or) more settings.

5. Symptoms that donot occur exclusively during the course of pervasive developmental disorder, schizophrenia or other psychotic disorder.

The practical consequence of these different diagnostic definitions is that the ICD-10 category of Hyperkinetic Disorder is a subgroup of ADHD described in DSM IV criteria **(Santosh, Taylor,Swanson et al)** [130]**.** Diagnosis is usually clinical using history taken from parent and atleast one other adult such as teacher or coach. There is no simple objective test such as blood test to diagnose ADHD.

EPIDEMIOLOGY

ADHD is the most common childhood psychiatric disorder affecting 5- 12% of children worldwide. **Polancyzyk et al** [115] estimated this prevalence using a meta-analysis which included about one lakh patients and 100 articles.

Prevalence rates vary in various cultural settings according to diagnostic criteria used to classify the disease and reported in a range of 1 -20%. (**Jensen 2005)** [67] . The male female ratio is 2:1 in community samples in contrast to 5:1 or 9:1 in mental health clinic sample (**Szatmari P et al)** [151]**.** Boys with ADHD have higher rates of disruptive behavior

(breaking rules) such as interference with teacher and classmates, distractability and both physical and verbal aggression than females (**Abikoff 2002)**[3]. Females present more often with less disruptive symptoms, more attention problems and problems such as depression and anxiety than males with ADHD . Male sex, low socioeconomic status and young age are associated with high prevalence of ADHD (**Biederman J)**[26]

Recent studies prove that ADHD symptoms continue into teenage and adulthood although previously it was proposed that ADHD symptoms wane off as the child reaches adolescence (**Pierce EW**[113] **et al)**

In India, few epidemiological studies are available for ADHD which report prevalence rates ranging from 10-20% . They have also shown that ADHD is more prevalent in boys than in girls. ADHD is more prevalent in lower socioeconomic class. (**Malhi P, Singh P et al)** [91]**.** It is also more common in nuclear families and behavioral problems are high in children from nuclear families(**Verghese A, Beig A)**[164]

AETIOLOGY

The aetiology of ADHD is complex and involves interaction between genetic and environmental factors during early fetal

development which creates a neurobiological susceptibility to this disorder. The expression of disease is mediated by alteration in different neural networks and neurotransmitters involved in mediating attention and executive functions**(Sonuga- Barke EJ)**[140.]

Prenatal, perinatal and post natal factors play a role in the pathogenesis of ADHD. Prenatal factors are associated with maternal lifestyle during pregnancy such as smoking and alcohol intake **(Linnet, Dalsgaard et al)** [86].

Maternal smoking has the strongest evidence among environmental factors and it increases the risk for ADHD by 2.7 fold. (**Milberger S et al**) [98]. There is a dose- response relationship between maternal smoking and ADHD. **(Thapar, Fowler, Rice et al)**[157].This may be due to the effect of smoking on nicotinic receptors which modulate dopamine which is involved in pathogenesis of ADHD**(Potter AS, Newhouse PA, Bucci)**[117] .Prenatal exposure to alcohol may lead to structural anomaly of cerebellum which is implicated in the pathogenesis of ADHD **(Coffin JM et al)**[39].Exposure to cocaine may lead to increased risk of ADHD**(Linares, Singer, Kirchner et al)** [85].

Seasonal predilection is associated with some cases of ADHD children who are born commonly in the month of September(winter) which may due to viral infections triggering the disease in genetically predisposed individuals(**Seeger G et al).**[132] Matenal stress during pregnancy may lead to ADHD due to increased cortisol secretion in stress**(Kapoor, Dunn, Kostaki et al)**[71]

Perinatal factors have also been implicated in ADHD. There is a two fold increase in ADHD in low birth weight children(**Bhutta, Cleves, Casey et al)**[25]. This effect is due to subtle lesions in frontosriatal circuit involved in pathogenesis of ADHD **(Carmody, Bendersky, Dunn et al)**[31]. Pregnancy and birth complications have been reported in mothers of children with ADHD**(Ben Amor, Grizenko, Schwartz et al, 2005)** [21].

Post natal factors include social and biological factors. Biological factors include a role for dietary deficiencies.

There is an imbalance of essential fatty acids such as omega-3 and omega-6 fatty acids which has been suggested in the pathogenesis (**Richardson, Montgomery, 2005et al**)[119]. Iron deficiency has been implicated in some cases of ADHD (**Konofal, Lecendreux,Arnulf et al**

2004)[74]. A role for artificial food additives in the aetiology of ADHD have been proposed in a randomized control trial but remains controversial (**Mccann, Barrett, Cooper et al 2007)** [96] . Idiosyncratic allergies and specific food allergies have been reported by some parents . Exposure to lead is associated with risk of hyperactive and inattentive behavior **(Levitt M 1999)**[84].

Social factors are also implicated in the aetiology in ADHD. Children experiencing parental neglect and abuse may be at increased risk of ADHD **(Glod and teicher, 1996).**[52] An English and Roman adoptees study has shown that these children were persistently hyperactive and inattentive even after adoption into another family before the age of 4 yrs **(Kreppner, O'Connor & Rutter, 2001)**[77]**.**

Genetic factors play an important role in the pathogenesis of ADHD. The mechanism by which they exert influence is not known **(Asherson, Kuntsi, Taylor 2005)**[16]. Family, adoption and twin studies show that ADHD is a highly heritable disorder**(Rietveld, Hudziak, Bartels et al)**[120]. Siblings of ADHD children show an eight fold increase in risk of ADHD **(Faraone and Biederman, 2000)**[48]**.** Biological relatives are at more risk than adoptive family members **(Sprich, Biederman,**

Crawford et al) [141]. According to twin studies, ADHD is one of the most heritable conditions accounting about 60 to 90% **(Thapar A et al)**[156]

Genes regulating neurotransmitter systems have been proposed to be involved in ADHD .Specific genes involved in the pathogenesis of ADHD were studied and these studies showed significant pooled effects for three polymorphisms of dopamine genes, the D4 and D5 receptors(DRD4 AND DRD5) and the dopamine transporter (**Faraone et al 2005)**[49] **(Thapar A et al**)[156]. DAT 1 and DRD4 are more likely to have functional significance out of these. There is no evidence for nor-epinephrine gene variants as of now but are under research. But DAT I association has been contradicted in a recent meta analysis(**Wohl, Purper- Ouakil, mouren et al 2005)**[169].

Based on animal knock out models an association of functional polymorphisms of serotonin transporter and receptor genes SLC6A4 and HTR 1B with ADHD has been suggested **(Faraone et al , 2005)**[49]. Genome scan studies on potential alleles for ADHD demonstrate linkage of chromosomes 5p13,6q12,16p13,17p11 and 11q22 – 25.

GENE ENVIRONMENT INTERACTIONS

Genes may interact with each other and with environmental risk factors to increase risk of ADHD in a non-linear manner so that genes of small effect show disproportionately larger manifestation of the disease when interacting with environmental factors **(Rutter, Moffitt & Capsi)**[125.]

Studies show that gene variants such as DRD4 and DAT 1 interacts with prenatal substance exposures in specific subtypes of ADHD.

Smoking is associated with combined ADHD in genetically susceptible children. **(Khan, Khoury, Nicholas et al)**[70]. Alcohol consumption during pregnancy is also associated with specific genes(**Brookes, Mill, Guindalini et al)**[30]**,** DAT 1 and DRD4 genes interacts with season of birth(**Seeger, Schloss, Schimidt et al)**[132].

PATHOGENESIS OF ADHD

The pathogenesis of ADHD involves three main concepts namely genetic aetiology, frontostriatal or executive dysfunction disorder and a catecholamine disorder. A change in concept of ADHD from a primary hyperactive disorder to an attentional disorder by DSM III R ,highlighted

neuro cognitive defects as the core pathology of the disease **(Castellanos, Sonuga- barke et al)**[34].

The concept of fronto-striatal/executive function disorder was proposed based on the similarities between people with ADHD and frontal lobe lesions **(Denckla, 2002)**[42].The circuit involved in this executive cognitive function is the Thalamo – cortico –striatal loop which consists of projections from the dorsolateral prefrontal cortex to the caudate nucleus of neostriatum which pass via a complex set of direct and indirect basal ganglia pathways through the thalamus and back to the prefrontal cortex **(Alexander &crutcher et al, 1990)**[5]. This circuit has connections to other regions such as the cerebellum, the parietal cortex, the dorsal anterior cingulated cortex, corpus callosum and the frontal motor cortex **(Timmann, D et al)** [159] **(Emond V, Joyal C, Poissant H)**[47]. Activity within this circuit is mediated by GABA and glutamate which is responsible for the background thalamo-cortical EEG activity which is modified by other neurotransmitters such as dopamine, norepinephrine and acetyl choline during stimulus related evoked responses and arousal mechanisms.

The prefrontal cortex functions in thinking and planning **(Mc.Geer et al, 1987)** [95]. It is described as attention association area and integrates body movements and behavior associated with attaining goals **(Posner & Peterson1990)**[116]. It operates in focusing the mind on specific tasks by screening out distracting sensory inputs in order to concentrate on a goal.

Basal Ganglia are masses of grey matter that lie lateral to the thalamus and involved in regulation of motor activity. Thalamus communicates with basal ganglia through neurotransmitter dopamine, brainstem relays information to basal ganglia via serotonin and acetyl choline mediates transmission from cerebral cortex to basal ganglia. Basal ganglia is involved in planning of movements and organization of goal directed behaviors. Basal Ganglia is found to be less active in children with ADHD (**Gabrieli, Brewer et al)**[50] .

Other than fronto-striatal executive circuit several extra-executive circuits have been implicated in the neurobiology of ADHD.

Toplak, dockstader & tannock [160] **et al, 2006** has implicated thalamo-cerebellar circuits in neural timing and temporal synchrony.

Sagvolden, johansen, aase et al.,(2005) [126]; SonugaBarke et al(2005)[140] has implicated orbitofrontal – ventral striatal circuitry in reward and motivation.

Banaschewski, Brandeis, Heinrich et al.,2004[17] has implicated posterior parietal network in attention, orientation and alerting response.

Anterior cingulate cortex is implicated in affective component of ADHD. Thus compensatory networks like insula and cerebellum are implicated in lower cognitive tasks in ADHD .**(Castellanos FX, Lee PP et al)[33]**

The evidence of catecholamine (dopamine and nor-epinephrine) dysfunction is indirectly shown by three observations.

1. ADHD symptoms are reduced by DA & NE agonists which act by different mechanisms to increase extracellular DA & NE **(Pliszka,2005)[114]**

2. There are a number of polymorphisms in gene affecting catecholamines especially dopamine**(Faraone et al,2005)[49]**

3. Lesions and knock out of genes related to catecholamines in animal models produce symptoms that mimics ADHD**(Arnsten and Li,2005)[15].**

The neurotransmitter dopamine is involved in motor control and feeling of well being. Dopamine transmission is found to be reduced in children with ADHD **(Castellanos et al)[34]**

EVIDENCES FAVOURING FRONTO-STRIATAL/EXECUTIVE FUNCTION HYPOTHESIS

Performance of children with ADHD is worse than controls in cognitive and executive functions such as response inhibition (ability to inhibit a response which is already initiated), delay aversion(a preference between a small immediate and a large delayed reward), interference control, planning and working memory **(Huang-Pollock&Nigg)[63].**

Nigg et al, 2005[106] conducted a study which showed that half of the children with ADHD showed a deficit in atleast one executive function.

MRI studies in children with ADHD have reduction in brain volumes up to 5% involving both gray and white matter.

Castellanos, Lee, Sharp et al[33] has shown reduction particularly in the dorsolateral prefrontal cortex and neostriatum (caudate nucleus and putamen).

Emond.V, Joyal.C & Poissant H et al [47] has shown reduction in volumes of and also corpus callosum ,dorsal anterior cingulate cortex and cerebellum.

Shaw, lerch, Greenstein et al., 2006 [133] have shown that cortical thinning is especially marked in prefrontal regions associated with executive control.

Shaw P, Rabin C et al[134] has shown a marked delay in cortical maturation in children with ADHD. The delay was associated with decreased cortical thickness in all regions of brain, especially Prefrontal cortex and right posterior parietal cortex. Children who continued to have ADHD symptoms in adulthood had thinner grey matter in the prefrontal cortex which persisted. Children who grew out of the disorder showed normalization of right posterior parietal cortex thickness which was initially thin.

Diffusion tensor imaging(DTI) is a modality of MRI which provides information about the direction and integrity of neural tracts in the brain.

D'Agati E, Caserelli et al[41] have conducted DTI studies in ADHD children and has shown developmental changes such as defective myelination in the white matter pathways surrounding basal ganglia and cerebellum. These changes cause a decrease in the speed of neural communication.

White matter abnormalities such as reduction in volume has been reported in ADHD children. **Silk et al**[136] **2008** in his study in 15 young males found white matter abnormalities in several regions underlying inferior parietal, occipito-parietal, Inferior parietal and inferior temporal cortex.

Durston, Tottenham, Thomas et al.,(2003) [45] have conducted functional MRI (f MRI) studies which showed reduced activity in ventrolateral and dorsolateral prefrontal cortex and **Rubia et al (1999)** [124] has shown reduced activity in neostriatum which includes caudate and putamen.

PET and SPECT show dynamic measures of brain metabolism at rest and during cognitive tasks and several studies have shown abnormalities in cerebral activation in ADHD with a hypo perfusion in frontal and striatal areas. Imaging studies using ligands highly selective for dopamine transporter which is involved in the pathogenesis of ADHD has shown that there is increase in DAT binding in the striatum of ADHD children.

Volkow ND et al[165] has done PET studies showing that methylphenidate hydrochloride blocks DAT and the extracellular dopamine increase is directly proportional to the level of blockade. This leads to increased perception of the external sensory stimuli in ADHD children.

CLINICAL FEATURES

Hyperactivity

This is the increase in activity which does not change with the set demands of the situation. So, children with ADHD are more active in the classroom and less active in the playground as compared to normal children. The level of gross motor activity decreases with age, but fidgetiness and inner sense of restlessness continues into adult life. Motor

difficulties include problems of sensory motor coordination such as poor hand writing, clumsiness and delay in achieving motor milestones. Motor impairment is associated in 50% of ADHD children. Motor problems are related to abnormalities in structure or function of cerebellum and basal ganglia.

Attentional Difficulties

ADHD children show several attentional difficulties. Cognitive functions such as problem solving, planning, orientation, alertness, response inhibition and working memory are impaired. They exhibit easy distractability, inability to sustain attention on a task, failure to follow instructions, inability to complete a task without constant supervision and forgetfulness in daily routines. Other domains involving affective components such as motivation , response inhibition and delay aversion are also involved **(Castenellos et al)[34] (Nigg JT et al) [106].**

Impulsivity

These children engage in dangerous activity, yells out in class, interrupts or intrudes on others during games or conversations. Impulsive behavior results in trouble with parents, teachers or other children resulting in physical or verbal fights. They respond very quickly without

thinking leading to decreased academic performance. This is due to internal pressure persuading the child to respond quickly.

Cognitive aspects

They have difficulty in time management and donot develop internal sense of pace in planning tasks. This poor time sense leads to problems in estimating actual difficulty waiting in a line and planning how much time a task requires.

Behavioral aspects

Children with ADHD lack persistence. They become bored and leave games early before they are finished. Other disabilities include temper outbursts, mood lability, greater intra individual variability of reaction time and cerebellar associated defects in motor timing .

Comorbidity

Considerable comorbidity in children occurs with conduct disorder, oppositional defiant disorder, mood and anxiety disorders and mental retardation **(Biederman et al)[27].**

Course of ADHD

Between 30 – 70% of children diagnosed as ADHD will continue to show symptoms as adults. In a study of adult ADHD, both genders had manifestation but females unlike in childhood situation were in majority and had higher rates of depression, anxiety disorders and conduct disorder than controls.(**Biederman et al 1996)**[26]

DIAGNOSIS

Since 1994, the diagnosis of ADHD has been most commonly made based on **DSM IV** criteria. Most children are referred because of impairment in academic performance, family or peer relationship. Although symptoms of gross motor overactivity declines with age, impairment due to inattention and impulsive behavior may continue into adulthood as adult ADHD. The presence of psychiatric comorbidity increases with age further complicating the clinical picture. ADHD is a diagnosis primarily made by history and various rating scales such as the Parent Teacher Rating scales for ADHD(Du paulGJ), the SNAP (Swanson) and Conner's revised long form(Conners). Additional diagnostic information can come from both positive and negative family history.

Mental status examination is done to rule out other mental disorders. Physical examination identifies soft neurological signs which include non focal motor deficits such as deficits in balance, motor planning and control and also deficits in sensory integration. Gustaffson et al, 2000 found a significant correlation between soft neurological signs and decreased cerebral blood flow measures in the frontal lobes bilaterally in children with ADHD. Inquiry about dietary intake and food allergy should also be done.

Electrophysiological studies such as EEG and Evoked Potentials are simple tools which aid in the diagnosis of ADHD. Several studies in ADHD children has reported changes which pose them as an important diagnostic tool.

EEG provide information about the background electrical activity of the brain. This study was first done in ADHD patients in 1938 by **Jasper HH** [66], Solomon P, Bradley when they mostly included qualitative EEG. With advancement in technology QEEG(Quantitative EEG) is used now not only for diagnostic purposes but also for biofeedback to improve attention.

Monastra (2000)[102] found that diagnosis of ADHD can be accurately made by the use of Q EEG procedures which measures electrophysiological activity in specific brain regions . The ratio of slow wave to fast wave activity (theta/beta ratio) is a developmental marker. Young children have high ratio which declines with age.

In ADHD children this ratio doesn't decrease with age and it is typically greater during tasks that demand focus.

Several QEEG studies have been done which have shown high theta/beta ratio in areas such as prefrontal cortex which is specifically involved in ADHD with high specificity and sensitivity.

EVOKED POTENTIALS

Evoked potentials are electrical potentials that occur in a group of neurons in response to stimulation of a sense organ which can be recorded by surface electrodes over the corresponding cortical areas. EPs are reliable measures of objective function of specific sensory pathways. They are very sensitive to detect abnormality even in a clinically normal subject and are highly specific in localizing the lesion in the particular component of the sensory pathway involved.

Event Related Potentials (Long latency potentials)

These are long latency evoked potentials evoked by endogenous stimuli which provide information about brain activity during cognitive tasks in response to auditory or visual stimuli and requires subject's attention and cooperation. They have a longer latency and higher amplitude and are not influenced by the intensity and frequency of stimulus. Due to the use of different types of performance indicators most of the studies related to ERP s are difficult to interpret.

Stimulus Related Potentials(short latency potentials)

These are short latency potentials evoked by exogenous stimuli which provide information about the integrity of neural pathways and neurotransmitter systems involved in interpretation of sensory stimuli presented to the individual which may be auditory, visual or tactile stimuli and they are independent of subject's level of attention and can be recorded even during sleep or anaesthesia. But they are influenced by frequency and intensity of the stimuli as opposed to Event related potentials.

ADHD and BAEP

Brainstem Auditory Evoked potentials may provide useful information about the integrity of auditory pathway and neurotransmitter systems involved in auditory transmission. It has been postulated that asymmetrical conduction of acoustic stimuli in the brainstem plays a role in the pathogenesis of ADHD **(Lahat E et al)**[79]. Defective auditory transmission may lead to defective attention in ADHD.A few studies have been conducted using BAEP in ADHD children and shows increase in amplitude and latency of several waveforms showing defective auditory transmission. BAEP can be used as a simple and cost effective physiological tool to assess auditory transmission.

Hannan Azzam et al [56] conducted an ABR study using click stimulus as well as speech stimulus and MMN on 15 Arabic speaking ADHD children and 15 age matched controls in the child/adolescent psychiatry clinic, Ain Shams University and found increased absolute latency of wave III and inter-peak latencies I-III & I-V in both ears in 33%(5/15) of ADHD children. Abnormal speech ABR was observed in 87% (13/15) ADHD children. The peak MMN latencies were prolonged with reduced amplitude.MMN component was absent in 40% (6/15).

A Puente et al [2]conducted a study in 18 school children diagnosed with ADD and compared them with 18 normal school children by recording both short latency auditory evoked response and long latency auditory evoked response and showed that brainstem conduction was significantly abnormal in children with ADHD. He found prolonged latencies of waves III & V and prolonged I-III & I-V IPL in ADD children as compared to controls. The latency of P300 was increased and mean amplitude was significantly decreased in children with ADHD compared to controls. He concluded that school children with ADD show significant abnormality in both Brainstem Auditory Evoked Response and Long Latency Auditory Evoked Response and so these electrophysiological procedures involving auditory pathway can be useful in diagnosis of children with ADHD.

Lahat et al[79] conducted a study in which he found prolonged wave III latency in females and prolonged wave V latency in both males and females. There was a prolonged I-III IPL in females and prolonged I-V IPL in both male and female subgroups. This result showed disturbance in the neural transmission in the auditory pathway. The latency of wave I is identical in both study and control groups showing that the abnormal

neural conduction in ADHD children is not due to abnormality in inner ear or eighth nerve.

NeelamVaney, MD et al [105]conducted a study on 20 male ADHD children and 20 age and sex matched controls in the Electrophysiology Laboratory of the Department of Physiology, University College of Medical Sciences, Delhi and showed that there were no statistically significant differences in the absolute peak latencies and amplitude as well as the IPLs of ABR waves in ADHD children as compared to controls.

Schochat E et al[131] conducted a study in 21 ADHD children and found that all children had normal ABR and normal latency for wave V. Some delayed P300 was found, some small and some absent. Among 42 ears combined 52.38% did not have P300. Medicated group had more presence of P300 than non-medicated group.

Ana Carla Leite Romero et al[9] in his article published in Brazilian Journal of Otorhinolaryngology has shown that when long latency auditory evoked potentials were measured in ADHD children using MMN & P300 there was significant differences in P2 amplitude in

LE which was higher for ADHD children and N2 amplitude and latency was abnormal in ADHD group.

Hilary Gomes et al [59]conducted a study to characterize the deficits in attention allocation in ADHD children. Findings for Nd, P3b and Ta in these children suggest that deficits in auditory selective attention in children with ADHD may be attributed to reduced information during early auditory processing. Nd waveforms were not elicited in children with ADHD and they exhibit significantly lesser auditory responses at 100ms (Ta).

The development of electrophysiological techniques such as EEG and Evoked potentials have passed through a series of interesting historical aspects after the introduction of electrodiagnosis based on faradic and galvanic current by **Erb** in 1861.

Richard Caton[118], a lecturer at Liverpool, UK had an idea that as the nerve impulse flows in and out of the brain, it may be detected at the surface and reported the findings in a meeting in British Medical Association in 1875. He demonstrated the effects of anoxia and anaesthesia on these potentials using optical magnification of movement of meniscus in Thompson's galvanonometer as electronic amplifiers were

not available at that time. He described EEG(Background electrical activity) as well as cerebral potential changes evoked by sensory stimuli(Evoked Potentials) and published his reports in British Medical Journal in 1877.

In 1929, **Hans Berger**, a German psychiatrist was the first to record EEG and documented brain waves using two scalp electrodes on his own son and named this spontaneous ongoing activity as "Des Electrenkephalogram".

In 1939 **Davis** recorded the first auditory evoked potential but the amplitude of this evoked potential was very small and it was **George Dawson** who discovered an innovative method of extracting the evoked potential from the ongoing EEG activity. First he used a photographic superimposition averaging technique to bring out EP wave form from back ground EEG activity and later he used an electronic summation technique which subsequently became the computerized averaging technique used today.

In 1967**, Sohmer and Feinmesser** were the first to publish ABR recorded with surface electrodes in humans and attributed it to brainstem

structures and showed that cochlear potentials could be obtained non-invasively.

The concept of far field potential was first developed by **Jewett** and in 1971, **Jewett and Williston** gave a clear description of human ABR wave forms and correctly interpreted the generation of the waves from brainstem. This short latency auditory response was first called as **Jewett bump** and now known as BAEP.

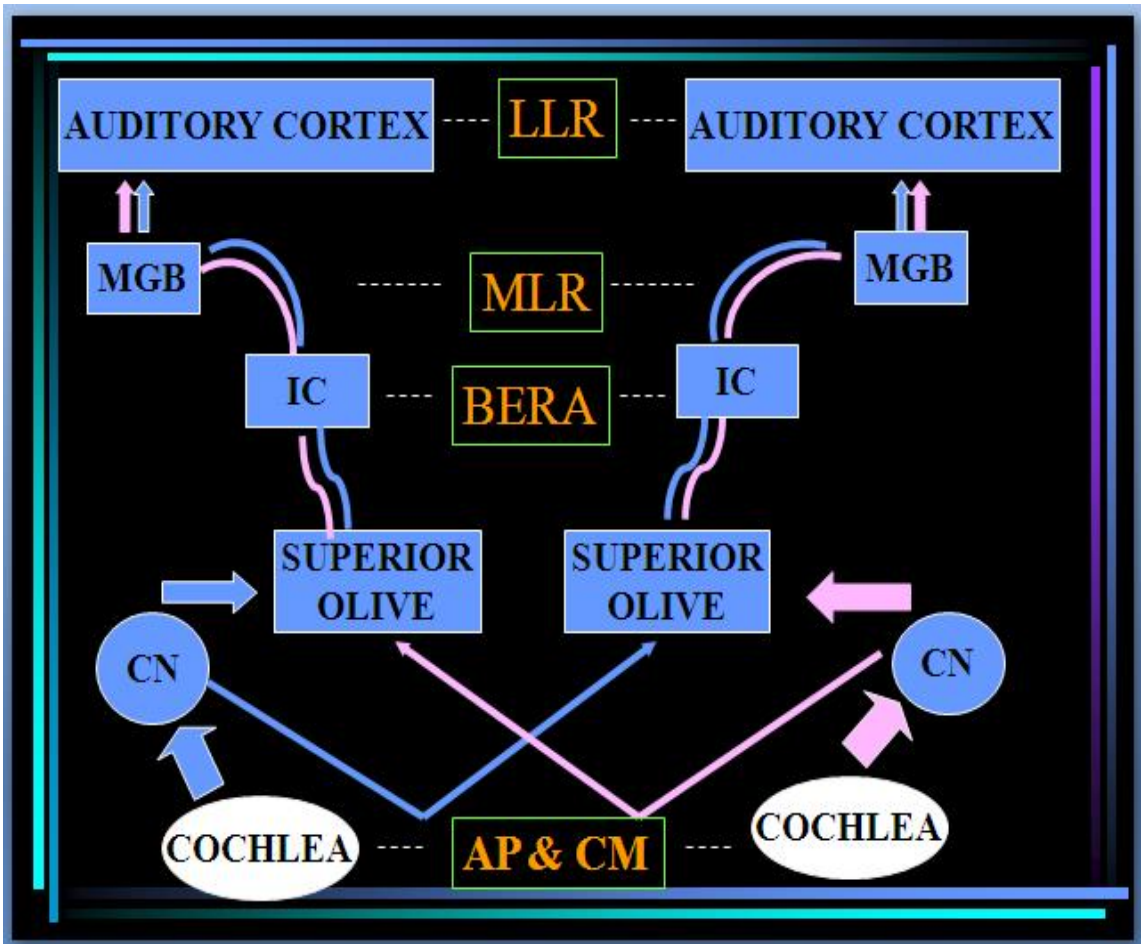
In 1974, **Hecox and Galambos** showed that ABR could be used for threshold estimation in adults and infants.

In 1977, **Setters and Brackman** published landmark findings on prolonged IPL in tumor cases.

BRAINSTEM AUDITORY EVOKED POTENTIAL

BAEP is an objective test of auditory brainstem function in response to auditory click stimuli which consists of seven positive waves recorded during the first 10 milliseconds after a click stimulus labeled as waves I to VII. The synonyms of BAEP include Auditory Brainstem Response (ABR), Brainstem Auditory Evoked Response(BAER),

FIGURE 3. GENERATORS OF VARIOUS AUDITORY EVOKED POTENTIALS



AP & CM - Action potential and Cochlear microphonics

CN - Cochlear nucleus

IC - Inferior colliculus

MGB - Medial Geniculate Body

MLR - Middle Latency Response

LLR - Late Latency Response

Brainstem Evoked Potential(BSEP), ABR audiometry, and Brainstem Evoked Response Audiometry **(Jiang et al) [68].**

The auditory evoked potential of first 10 millisecond after the acoustic stimulus is called the short latency response (SLR). The SLR is popularly known as brain stem auditory evoked potentials (BAEP), since it records the auditory evoked potential when the auditory stimulus is traversing through the brain stem region. The middle latency response (MLR) is the transient response that occurs in the 10- 50 milliseconds post-stimulus time and the late latency response (LLR) is the response recordable in the 50-300 milliseconds post-stimulus period (**Picton TW et al)[112].**

ANATOMICAL AND NEUROPHYSIOLOGICAL BASIS OF BAEP[83]

The sound pressure wave produces displacement of the tympanic membrane which is transmitted to the oval window through the inner ossicles. This produces movement of the perilymph (contained in the scalavestibuli and scala tympani, which are joined at the apex of the cochlea by the helicotrema) and then secondarily of the endolymph, which is present in the ductus cochlearis or scala media which includes the basilar membrane, spiral organ, and the tectorial membrane. The

spiral organ contains hair cells that, when displaced by the movement of the tectorial membrane, produces auditory potentials. The receptor potentials leads to the release of the neurotransmitters, which trigger action potentials in the dendrites of the afferent nerve fibers of the cochlear nerve. There are 20,000-30,000 hair cells distributed over a distance of approximately 31.5mm in the 2.5 spirals of the cochlea. High-frequency sounds activate the basal portion of the basilar membrane where as low-frequency sounds generate receptor potentials in the apical portion of the cochlea. The click, which is the most commonly used stimulus to produce Brain stem auditory evoked potentials (BAEPS), contains mainly high-frequency components and mainly activates the basal portion of cochlea.

The cochlear nerve neurons are bipolar, situated in spiral ganglia and their dendrites go to hair cells and axons to the cochlear nucleus.

The cochlear nucleus has three sub-nuclei:

1. Anterior ventral cochlear nucleus (AVCN)
2. Posterior ventral cochlear nucleus (PCVN)
3. Dorsal cochlear nucleus(DCN)

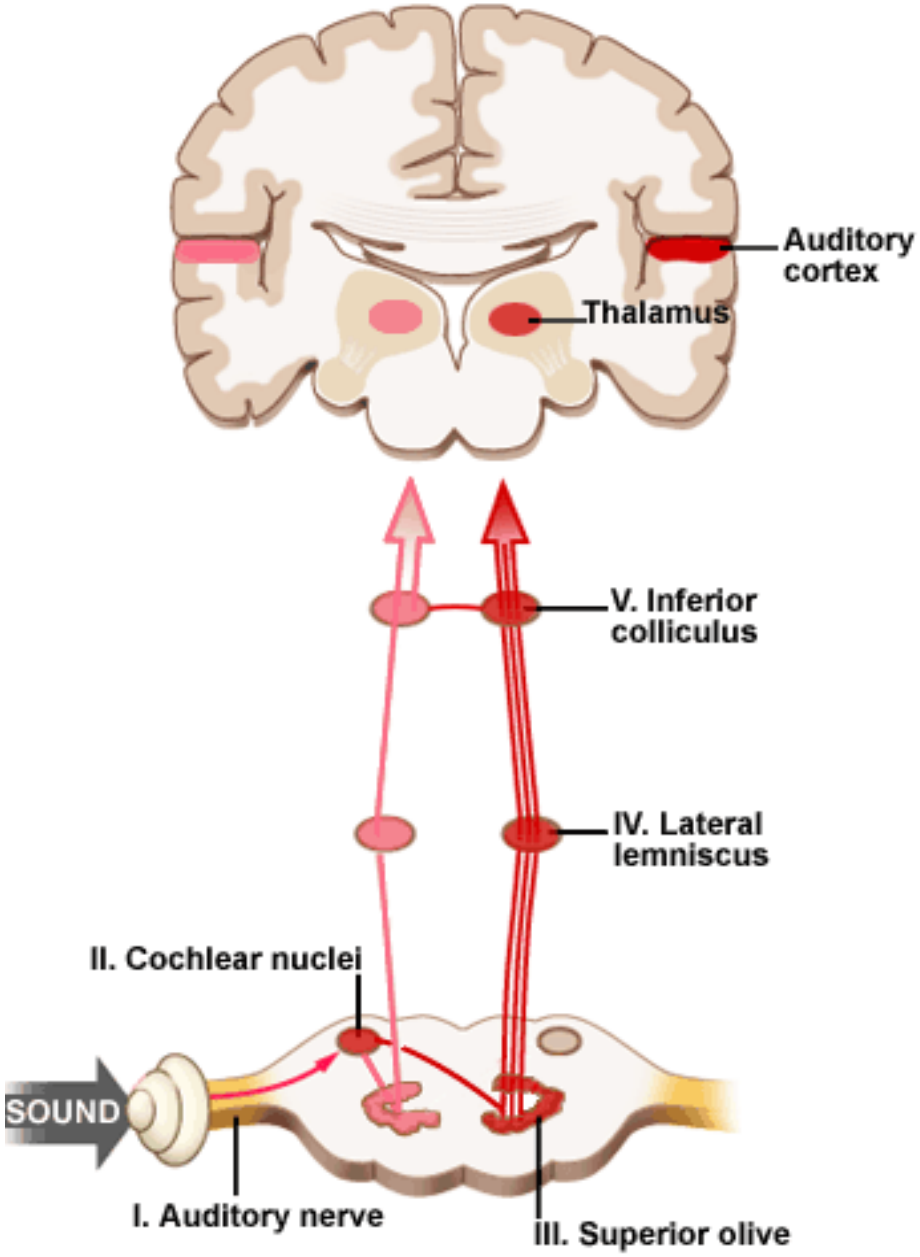


FIG-4 AUDITORY PATHWAY

The output of AVCN is through the ventral acoustic striae forming the bulk of trapezoid body to terminate in the superior olivary nuclei and inferior colliculus. The neurons in the AVCN discharge at short latency to acoustic stimuli with a pattern like that of cochlear nerve.

The output of PVCN mostly goes through the ventral and middle acoustic striae to terminate in the superior olivary nuclei and inferior colliculus.

DCN output terminates in the superior olivary nucleus and contralateral inferior olivary nucleus through dorsal striae, The discharges from these neurons are different from those of AVCN by having longer latency.

The cochlear nuclear complex thus terminates in the superior olivary nuclear complex, which has medial and lateral components at the base of the pons. The medial superior olivary nucleus receives the input from both ipsilateral and contralateral AVCN which are excitory. The lateral superior olivary nucleus also receives ipsilateral excitatory inputs from AVCN and PVCN and inhibitory inputs from contralateral AVCN and PVCN via trapezoid body. From the olivary nuclear complex, the impulses travel to ipsilateral and contralateral lemnisci and to inferior

colliculi. The olivary nuclei are the first in the auditory pathways where the neurons are affected in a non-linear manner to binaural stimulation.

The inferior colliculi and the lateral lemnisci converge the input from contralateral cochlear nucleus and superior olivary nucleus. The impulse from inferior colliculus travels to medial geniculate body. Neurons in the medial geniculate body form the acoustic radiation of the internal capsule, synapsing in the Heschl gyrus of the primary auditory cortex (superior temporal gyrus and upper bank of sylvian fissure including the frontal and parietal opercula). High frequency tones, such as clicks, activate mainly the deeper most mesial portion of the heschl gyrus.

The orderly orientation of the neurons in dorsal cochlear, medial and lateral superior olivary nuclei results in summation of synaptic potentials which results in high amplitude electrical fields.

As the auditory impulses travels through the different components of the auditory pathway, it undergoes some degree of processing at each level. Passage of the impulse through this pathway generates an electrical activity which can be monitored by placing a surface (far –field) electrode on the vertex of the scalp. On graphic recording, this electrical

activity presents a waveform with discrete peaks, the character of which is dependent upon the structural and functional integrity of the above mentioned auditory pathway.

BAEP is produced by presenting auditory stimuli to each ear which results in a sequence of waveforms that bear a close relationship to the auditory pathway structures (peripheral, pontomedullary, pontine and midbrain) and so allows specific localization of pathology in the auditory pathway. BAEPs are recorded within 10 milliseconds of the acoustic stimulus

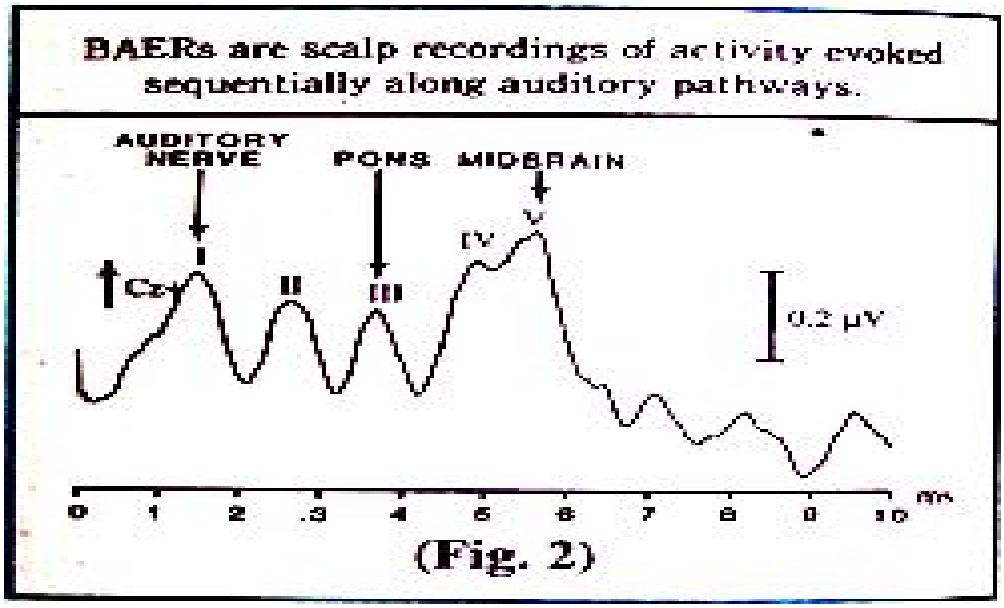


Fig. - 5 Normal Auditory Evoked Potential Wave Pattern

FIGURE : 6

ORIGIN OF BAEP

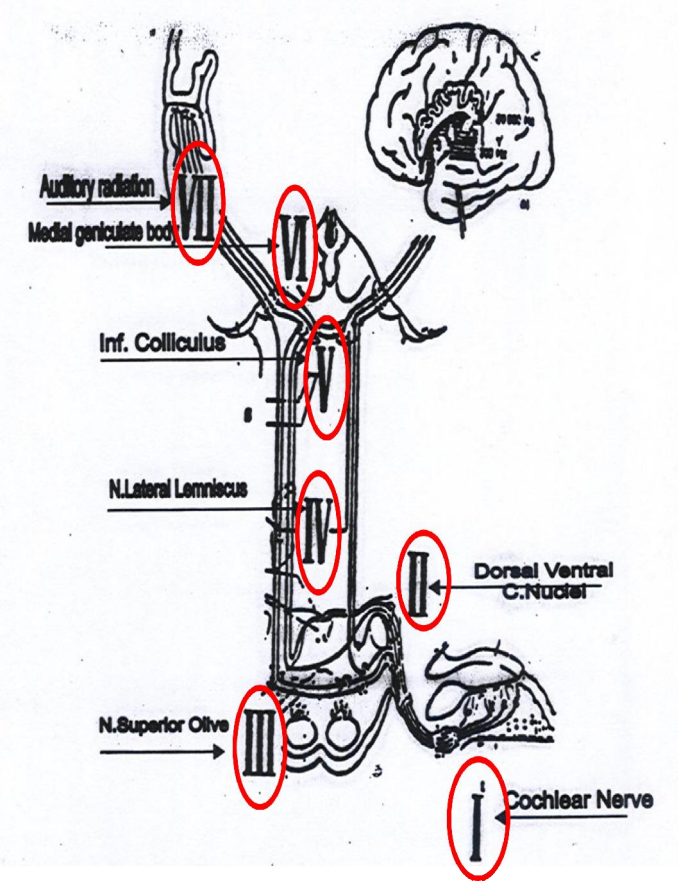


TABLE NO.1

Generators of BAEP waveforms **(Chiappa 1990)**[36]

Waveform	Generators
I	Cochlear nerve
II	Cochlear nucleus
III	Superior olivary nucleus
IV	Lateral lemniscus
V	Inferior colliculus

CLINICAL APPLICATIONS OF BAEP [29,99]

BAEPs have widespread clinical application in assessing both neurologic and audiologic problems. It is used in

1. Detection of deafness in difficult-to-test patients like infants and mentally retarded or malingering subjects in whom required response will not be available for subjective pure tone audiometry test. This test can be carried out correctly even in deeply sedated and anaesthetized patients.

2. Objectively determining the nature of deafness (i.e., whether sensory or neural) in difficult-to-test patients, especially in circumstances when the patients cannot follow or respond adequately to tests.

3. Identification of the site of lesion in retro-cochlear pathologies. The retro-cochlear pathology is a fairly big area from the spiral ganglion of the cochlear nerve to the midbrain (level of inferior collicullus). The other tests allow the neurotologists to merely suspect whether any retro-cochlear disease is present or not, whereas the BERA test helps us to delineate the approximate area in the retro-cochlear pathway where the lesion is present. This

helps in diagnosing conditions like acoustic neuroma and other CP angle tumors with precision and accuracy.

4. Diagnosis of demyelinating disorders such as multiple sclerosis.

5. Study of central auditory disorders. Evoked response audiometry has been found to be of use in separating disease of the auditory cortex from disease of the more peripheral organs.

6. Study of maturity of the central nervous system in newborns. It is an effective screening tool for hearing in the newborn with sensitivity of 100% and specificity of 96-98%

7. For objective identification of brain-death and assessing prognosis in comatose patients.

8. For intraoperative monitoring of eighth nerve and brainstem function during posterior fossa surgery**(Markand, 1994)**[93]

Although the AEPs parallel hearing, they do not test hearing per se; rather, they reflect a synchronous neural discharge in the auditory system. Thus, an individual may have a normal behavioral audiogram and a grossly abnormal AEP and central auditory deafness.

Researchers have recently focused on nutritional issues to understand mental health problems. Evidences for the role of micronutrients in mental health has come from studies focusing on role of zinc in ADHD **(Ann M Di Giralamo et al)**[10]. Animal and human studies show relationship between low serum zinc concentrations and symptoms of ADHD and suggest improvement of symptoms with zinc supplementation.

Zinc is a trace mineral that is involved in RNA and DNA synthesis and it is very important for cellular growth, differentiation and metabolism **(Sanstead HH et al)**[129]. It is also essential for brain development and central nervous system function. More than 200 enzymes are zinc metalloenzymes requiring zinc for normal development of neurons. Zinc deficiency can interfere with function of multiple organ systems particularly when it occurs at times of rapid growth and development during which period there is high nutritional demand.

The normal zinc intake is about 10-15 mg/day and is excreted mainly in the faeces through the intestine. The total zinc content of the body is about 2 – 2.5 gms with no tissue stores. The highest zinc content is present in the muscles, the bones, liver, male reproductive organs, eyes

and hair. The normal serum zinc level is 80 - 170µg/dl with an average of 124 ± 16µg/dl. Zinc from meat sources have higher bioavailability than vegetarian sources due to presence of aminoacids which enhance zinc absorption. ADHD children in general have specific liking to vegetarian foods rather than non-vegetarian foods and this may be another reason for their zinc deficiency.

Zinc contributes to behavioral changes such as focusing attention and reducing aggressiveness through regulatory effects on certain brain neurotransmitters such as melatonin and fatty acids. The prevalence of zinc deficiency in ADHD children is about 26% as opposed to 3.3% prevalence in the normal children **(Joy Y Kiddie)**[69]. Several studies have shown that children with ADHD are more likely to have zinc deficiency than other children. One of the studies have shown that taking zinc supplements can reduce the symptoms of ADHD.

Zinc status is traditionally assessed **(Sandstead & Alcock 1997)**[128] using plasma& serum assays. This can detect severe as well as marginal zinc deficiency, but it has two limitations. Plasma zinc is not always sensitive to small changes in chronic zinc status **(Thompson, 1991)**[158] and serum zinc values are affected by inflammation and physiological

stress. So researchers use dietary restrictions to assess consequences of zinc deficiency in animals. Several studies using rats, mice and monkeys have examined relation between zinc concentration and behaviors such as aggression and attention. Studies in prepubertal monkeys with moderate dietary restriction of zinc shows reduced spontaneous motor activity and reduced performance of tasks **(Golub et al)**[53]. Studies have shown more aggressiveness in zinc deficient rats compared to control rats. In humans the role of zinc in ADHD is assessed by supplementation of zinc in specific doses and observation of improvement of ADHD symptoms in suspected zinc deficient ADHD population.

BIOLOGICAL EFFECTS OF ZINC

1. Zinc is essential for wound healing. In the form of zinc oxide it is used in the treatment of diaper rash **(Patel GK., Harding KG)**[110]

2. Hypothesized to play a role in treatment of inflammatory acne and is present in many nutritional supplements for acne **(Dreno B.,Moyse D et al)**[44]

3. Zinc sulphate combined with vit c is being used in treatment of bed sores.

4. Zinc is known to boost up immunity and it is used in chronic herpes infection **(Chien XX et al)**[37]

5. Zinc lozenges are under trial for common cold.

6. Zinc preparations are used to hasten up recovery from diarrhea.

7. Plays a role in limiting inflammation

8. It's role is being explored in Alzheimer's disease.

9. It plays an important role in fertility of males and also required by females for ovulation.

10. Studies have shown that Diabetic neuropathy improves with zinc supplementation as evidenced by improvement in nerve conduction studies **(Hayee MA., Mohammerd QD., Haque A)**[58]

11. Zinc has been shown to be effective in the treatment of Age related macular degeneration.

12. Zinc increases the response to treatment with conventional stimulant treatment in ADHD children Sources rich in zinc include oysters, sea food, beef, chicken, pork, nuts and whole grains.

ROLE OF ZINC IN THE PATHOGENESIS OF ADHD

Several mechanisms have been suggested to explain the role of zinc in the pathogenesis of ADHD. Most of the mechanisms possibly acts through alterations in neurotransmitters such as dopamine and serotonin involved in the pathogenesis of ADHD.

Zinc is a cofactor for metabolism of several neurotransmitters such as dopamine and prostaglandins and thus affects dopamine which is involved in the pathogenesis of ADHD indirectly **(Toren et al, 1996)**[161]

Zinc is essential for the production and modulation of melatonin which regulates dopamine function **(Chien XX et al)**[37]**.** There is a proposal that parasympathomimetic stimulants act in ADHD partly through its effect on melatonin. Dopamine transporter (DAT 1) which is involved in the degradation of dopamine has an endogenous zinc binding site on binding to which zinc acts as a non-competitive blocker and prevents dopamine binding to the transporter and thus increases the availability of extracellular dopamine by decreasing its degradation **(Lepping P. Haber M)**[82]**.**

Zinc is essential for the conversion of dietary pyridoxine to its active form, pyridoxal phosphate which is necessary for conversion of

tryptophan to serotonin **(Bilici M et al)**[28]. As both dopamine and serotonin neurotransmitters are implicated in ADHD (Quist JR) supplementation of zinc deficient ADHD children with zinc may improve the levels of deficient neurotransmitters and thus improve ADHD symptoms of impulsivity **(Bilici M et al)**[28] **(Arnold LE, Di silvestro RA)**[11]**.**

Zinc may also influence the N2 wave in the frontal and parietal regions of the brain with effects seen on information processing and on inhibitory processes in the CNS which is affected in ADHD children. Evidences show increase zinc ion release during neuronal activity **(Li et al., 2003)**[87]

Zinc is essential for maintaining the neuronal structure by affecting the metabolism of polyunsaturated fatty acids (PUFA) which are the building blocks of neuronal membranes **(Black 1998)**[23]. It acts as a cofactor for the enzyme delta-6-desaturase which is involved in the anabolism of PUFA that constitute the neuronal membrane **(Bettger et al, 1979)**[22]

Zinc interacts with Essential Fatty Acid metabolism in a number of ways **(Bekaroglu et al, 1996)**[20]. EFA is a substrate for the enzyme

delta-6-desaturase which modulates cyclooxygenase activity **(Sakuma[127] et al, 1996)**. Cyclooxygenase is required for production of prostaglandins and thromboxanes from EFA precursors which inturn facilitate zinc absorption **(Song & Adham ,1980)[139]**. EFAs are involved in dopamine and norepinephrine implicated in the pathogenesis of ADHD **(Molderings et al,1992)[101]**. A significant correlation is seen between serum zinc and FFA levels in patients with ADHD who had lower levels of both serum zinc and FFAs than the healthy controls **(Bekaroglu et al)[20].** Thus EFAs and zinc play a synergistic role in the regulation of dopamine, norepinephrine and probably serotonin and so zinc and fatty acids supplementation may be beneficial in improving symptoms in the deficiency group.

Kozielec et al(1994)[76] in Poland showed that serum zinc levels were significantly lower in ADHD children compared to healthy controls.

Toren et al(1996)[161] in Israel reported significantly lower serum zinc levels in a group of 39 boys and 4 girls with ADHD in the age group of 6-16 yrs compared to 28 age matched controls. About 30% of ADHD children had serum zinc levels in the lower range compared to controls. It was suggested that the ADHD symptoms of hyperactivity was due to zinc

deficiency and did not respond to amphetamine but improved with zinc supplementation.

Bekaroglu et al(1996)[20] in Turkey recorded low mean serum zinc levels in 48 children(33 boys and 15 girls) with ADHD compared to healthy controls(30 boys and 15 girls). He evaluated the relationship between FFAs, zn and ADHD in the two groups and found statistically significant decrease in FFAs and zinc levels in ADHD children. He concluded that zinc deficiency may have a role in the pathogenesis of ADHD.

Starobrat-Hermelin et al(1998)[142] in Poland reported deficiencies of zinc, magnesium, iron, copper and calcium in 116 ADHD children by analysis of serum, red blood cells and hair. Hair zinc levels were lower in ADHD with comorbid conditions like ODD or conduct disorder than in children with ADHD alone.

Arnold et al (2005)[12] in an American study reported that severity of ADHD symptoms were related to serum zinc concentration. He showed that serum zinc correlated with parent and teacher rated inattention but not with Hyperactivity and impulsivity in US children

with ADHD where as a similar study in Turkey showed serum zinc correlation with hyperactivity rather than inattention.

Sandstead et al(1997)[128] reported that Chinese children with marginal zinc deficiency as evidenced by serum levels showed improvement in neuropsychological performance on zinc supplementation.

Orner et al, (2010)[109] showed that low serum zinc and ferritin levels were associated with higher hyperactivity symptoms in children with ADHD.

Magdy M. Mahmoud et al[89] in Egypt showed that serum zinc, ferritin and magnesium levels were significantly lower in children with ADHD than normal controls but there was no significant difference in copper levels.

Arnold et al (1990)[14] showed that 18ADHD children had 30% lower 24 hours urine zinc than 7 normal controls. He projected that this could be due to low dietary intake or absorption rather than zinc wasting metabolism.

Akhonzadeh et al(2004)[4] showed that zinc supplementation of ADHD children along with conventional stimulant drugs like methylphenidate (MPH) increases the response to drugs. Study in 44 Iranian children with ADHD of age 5-11 yrs showed significant improvement in ADHD children who were supplemented with zinc along with MPH rather than with MPH and placebo.

Arnold et al[13] found that response of a group of 6-12 yrs boys with ADHD to the drug amphetamine was related to zinc concentration. Stronger response was seen in children with adequate zinc concentration. In another placebo controlled pilot study of zinc alone and combined with amphetamine , he showed that clinical effect of zinc was equivocal except that there was a 37% decrease in dose of amphetamine.

Bilici et al[28] in Turkey showed that zinc sulphate was statistically superior to placebo in reducing both hyperactive and impulsive symptoms and impaired socialization but not inattentive symptoms. He found that the scores decreased significantly inpatients of older age and high BMI score with low serum zinc and FFA levels.

J. Gordon Millichap et al [64] found that low zinc levels are seen in serum, red cells, hair, urine and nails of ADHD children.

Mikirova et al[97] suggested that correction of serum zinc levels in ADHD children improved the behavioural responses.

Ward et al(1990)[166,167] suggested a possibility of exacerbation of marginal zinc deficiency by food additives and other chemical interactions. He challenged 10 hyperactive boys and 10 controls with tartrazine containing commercial beverages and found that serum and saliva zinc decreased while urine zinc increased in hyperactive and not the control boys which suggests zinc wasting from the body due to dye challenge.

Halas et al[55] examined zinc deficiency in rats during infancy period by depleting zinc levels during the period of development and then replenishing them with zinc rich foods and then examined their behavior in adulthood. Early severe zinc deficiency leads to increased emotionality in adulthood.

Sandstead et al (1977)[129] studied the effect of zinc deficiency on behavior of rats and rhesus monkeys and showed association of ADHD symptoms with zinc deficiency.

Golub et al[53] reported impairment of attention at levels that did not cause growth retardation. He also showed that short term zinc deprivation

in prepubertal monkeys resulted in reduced motor activity and less accurate performance on measures of attention and short term memory.

Arnold et al(2005)[11] reviewed published evidences for the role of zinc in ADHD and reported its limitations and concluded that many children with ADHD have lower serum zinc levels than normal controls, zinc nutritional status may interact with food additives and two mid-eastern trials showed greater improvement with zinc supplements than with placebo.

Animal and clinical trials implicate deficiencies of zinc as an essential cofactor in neurotransmitter, prostaglandin, and melatonin metabolism and thus in ADHD pathophysiology.

The literature and studies reviewed here show that reduced serum zinc levels could be markers for EFA deficiency which is the substrate for prostaglandins required for zinc absorption **(Song and Adham)**[139] or they could be markers for general malnutrition **(Wesnes et al)**[168]. Zinc levels could be markers of a gene that results in decreased absorption of zinc or it could be marker of inflammation during which zinc levels are decreased suggesting immune problems **(Shenkin 1995)**[135]. Decreased

zinc levels could be due to exacerbation of marginal zinc deficiency by food additives, drugs or other chemicals.

Thus from the above facts we can infer that

1. Many ADHD children have lower zinc levels compared to healthy controls.

2. Ingested chemicals such as food additives may interact with zinc nutritional status and may cause zinc deficiency

3. Zinc supplements improve symptoms of ADHD in zinc deficient children. Several clinical trials are expected in the future to elucidate the role of zinc in ADHD as a monotherapy, as an adjunct to stimulant treatment and also to evaluate the relationship of other nutrients to zinc and the effect of food additives on zinc levels which will be beneficial to the community. Thus in the present study work is undertaken to study the levels of serum zinc in ADHD children and find out if zinc has been involved in the pathogenesis of ADHD, with the aim of reducing the incidence of ADHD that may occur as a result of zinc deficiency.

Serum zinc levels can be measured by Atomic Absorption Spectrophotometry or colorimetric methods.

Aim and Objectives

3. AIM AND OBJECTIVES

AIM

To assess the central auditory processing using Brainstem auditory evoked potential and to measure serum zinc levels in children with Attention Deficit Hyperactivity Disorder in comparison with age and sex matched controls.

OBJECTIVES

1. To assess the brainstem auditory evoked potential in children with Attention Deficit Hyperactivity Disorder (ADHD).

2. To determine the role of brainstem auditory evoked potential in the pathophysiology of ADHD

3. To compare the serum zinc levels of children with ADHD and normal children.

4. To correlate serum zinc levels with brainstem auditory evoked potential

Materials & Methods

4. MATERIALS AND METHODS

The study was conducted between March 2014 to August 2014 in the INSTITUTE OF PHYSIOLOGY AND EXPERIMENTAL MEDICINE, MADRAS MEDICAL COLLEGE after receiving the approval from the Institutional Ethical Committee, Madras Medical College, Chennai.

SUBJECT SELECTION

Thirty male children between 6-11 yrs diagnosed with ADHD, according to DSM IV criteria and getting treatment were selected from the Child Guidance Clinic, Institute of Child Health, Egmore, Chennai-600 008 to participate in the study and thirty age matched apparently healthy male children selected from community were the controls. Informed consent was obtained from the parents of ADHD children and also controls.

PATIENT SELECTION

Diagnosis of ADHD was made using DSM IV criteria according to which ADHD is divided into three subtypes namely predominantly inattentive type, hyperactive-impulsive type and combined type. Ten male children from each of the three subtypes accounting to a total of 30

were selected for the present study from the children attending the Child Guidance Clinic in the Institute of Child Health. Assessment was done using Parent Rating Scale and Vanderbilt ADHD Diagnostic Teacher Rating Scale. IQ Assessment was done using the Malin's Intelligence scale for Indian Children (MISIC). Only children with IQ equal to or greater than 90 were selected for the study.

INCLUSION CRITERIA

Children in the age group of 6-11 yrs diagnosed with ADHD.

EXCLUSION CRITERIA

Children with

Autism, Pervasive developmental Disorder**,** perinatal hypoxia, Developmental delay, Epilepsy, CNS infection, Demyelinating disorders, Hearing disability, chronic medical illness, Malabsorption, General malnutrition, other psychiatric disorders.

STUDY DESIGN	**:**	Cross sectional study
TYPE OF STUDY	**:**	Comparative study
PLACE OF STUDY	**:**	Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai – 3. Institute of Child Health, Egmore, Chennai – 8.

HISTORY

Detailed history was collected from the parents of both controls and ADHD children. This includes information regarding birth complications such as preterm delivery, perinatal hypoxia and family history of ADHD and other psychiatric and neurological disorders. Enquiry should also be made about the socioeconomic status as ADHD is found to be common in low socio-economic status. In addition dietary history and history of allergy to foods containing additives should also be collected.

CLINICAL EXAMINATION

Common For Both Study and Control Groups

Regular anthropometric measurements (height and weight) were taken in both groups. BMI was calculated using the formula weight in kg/height in cm^2 and BMI percentile was compared between normal healthy children of same age and sex **(Must et al[104])**

BMI between 5^{th} and 85^{th} percentile is normal.

BMI between 85^{th} and 95^{th} percentile is overweight.

BMI less than 5th percentile is underweight.

BMI greater than 95th percentile is obese **(Himes & Dietz 1994[60])**

Vitals (Pulse, BP, Respiratory rate and temperature) were measured.

General examination of the subjects of both groups were done. Systemic examinations including cardiovascular system, Respiratory system and Central Nervous system including Cranial Nerve examinations were done.

For the study group, these basic clinical examinations were done in Institute of Child Health. For the control group, these clinical examinations were done in the Institute of Physiology and Experimental Medicine.

SPECIFIC ENT EXAMINATION

Both the groups of the subjects were subjected for specific ENT examinations in the Upgraded Institute of Otorhinolaryngology, Madras Medical College, Chennai.

The ENT examination includes external ear examination, turning fork tests which include Rinne's Test and Weber's Test, otoscopic

examination of tympanic membrane, presence of any obstruction by wax and examination of throat and nose.

If there is any presence of obstruction by wax, it was promptly dissolved by appropriate treatment before subjecting them for Pure tone Audiometry.

PURE TONE AUDIOMETRY

Both the group of subjects were subjected for Pure Audiometry in the Upgraded Institute of Otorhinolaryngology.

This is done to

i. Know the hearing threshold of the subjects.

ii. To rule out any external or middle ear pathology {integrity of conductive pathway}

PRINCIPLE AND METHOD OF PURE TONE AUDIOMETRY[88]

This is the most commonly used method of measuring hearing acuity. A pure-tone audiometer is an instrument which delivers tones of variable frequencies and intensity to the ear by ear phone. The frequencies usually tested are at octave steps, i.e. 125, 250, 500, 1000,

2000, 4000 and 8000 Hz. Occasionally half octave steps, such as 1500, 3000 and 6000 Hz area used. The intensity can be increased or decreased for each frequency and can vary from 10 dB to 120 dB. Most audiometers used today are calibrated to the International Standard Level (ISO).

Both the air conduction and bone conduction can be measured and are done in the same manner. The best frequency to start with is 1000 Hz. A series of short signals or tone-pips are put in at intensity above the patient's suspected threshold and the patient is instructed to signal every time he hears a sound. The intensity is reduced in 10 dB steps until no sound is heard. The signal is then increased in 5 dB steps until half of the tone pips are consistently heard. This is the patient's threshold for that frequency. The thresholds for the remaining frequencies are then measured. The bone conduction is measured in a similar fashion by putting a receiver onto the mastoid bone. The sound emitted by this is transmitted by the bones of the skull to the cochlea, thus bypassing the external and middle ears and giving a measure of inner ear function. The results are charted as audiograms.

In audiometry, it is important to eliminate the possibility that the test sound is being heard in the opposite ear. Masking must be applied to

the better ear when testing the deafer ear if the difference in threshold is found to be 40 dB or more. When testing the bone conduction threshold, the other ear should always be masked because of the ease with which bone conduction sound is transmitted through the bones of the skull.

BRAIN STEM AUDITORY EVOKED POTENTIAL

Both the groups (ADHD children and normal children) were subjected to non-invasive assessment of hearing and central auditory processing of stimuli i.e., by Brain Stem Evoked Response Audiometry (BERA) /Brainstem Auditory Evoked Potential (BAEP) /Auditory Brainstem response(ABR).

PRINCIPLE OF BAEP

A brief auditory stimulus generates action potentials in the auditory pathway which are recorded from the ear and vertex as BAEPs. The evoked response audiometry is based on the principle that the bioelectric response evoked by a sound stimulus always occurs after the same time interval **(Lau S. K. & William I. Wei)**[81]

PHOTO NO.1

COMPUTERISED NEUROSTIM MEDICAID SYSTEM FOR RECORDING BAEP

APPARATUS FOR BAEP

The apparatus set up for measuring BAEP are set as per the "Recommended standards for the clinical apparatus for practice of Evoked Potentials, introduced in **guideline 9A**[7]: Guidelines on evoked potential, by American Society of Clinical Neurophysiology.

The apparatus for BAEP used in our study is NEUROSTIM of Medicaid Systems

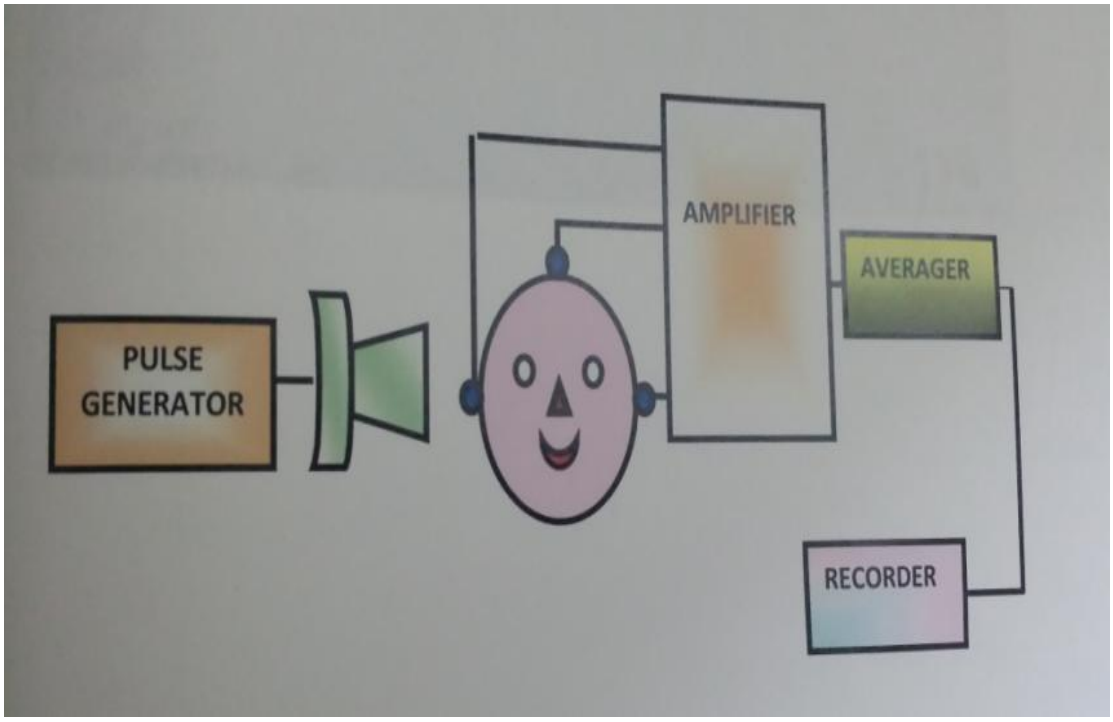


FIGURE : 7

PULSE GENERATOR

The stimulus is either in the form of clicks or tone-pips and is transmitted to the ear via a transducer placed in the insert ear phone or head phone. The click stimulus is a square wave pulse of 0.1 ms duration. The stimulation of contralateral ear is prevented by masking it with a white noise of about 30-40 dB.

RECORDING ELECTRODES

The electrodes required for BERA measurement are placed in the corresponding sites of the scalp following the International 10-20 Electrode placement system. High quality EEG electrodes are used. Both needle and surface electrodes are used for recording BAEPs. Surface electrodes are preferred because it is painless and there are lower chances of infection.

For better placement of electrodes, the hair must be oil free. The patient should be instructed to have shampoo bath before coming for investigation. 1cm disc electrodes filled with conducting jelly or paste is preferred. The electrical impedance should be kept below 5 kilo ohms. If the impedance is too high, the skin is cleaned again with acetone and the surface electrode is reapplied together with electrode jelly or EEG paste.

Active and ground electrodes are placed on the ipsilateral and contralateral mastoid processes respectively, after the skin has been cleaned. The electrode on the vertex acts as the reference.

FILTER

Filter is a device, which selectively restricts the frequency domain of a signal. The filter band pass is the frequency range of a signal, which is transmitted through the filter. The frequency range in which the signal is rejected is known as stop band. Filtering of neurophysiological signals is required for eliminating the noise and optimising the recording. Filtering is also useful for bringing out the characteristics of the waveforms.

The low frequency filter removes the slowly changing low frequency components and allows the higher frequencies to pass through. Therefore, the low frequency filter is also known as high pass filters. Similarly, the high frequency filter eliminates the rapidly changing high frequency components and allows the low frequency component to pass through. Hence the high frequency filters are known as low pass filters.

Filter setting for BERA is as follows;

Low – cut filter: 10 – 100 Hz.

High – cut filter: 3000 Hz.

AMPLIFIER

Since the biological signals are very small (5 to 50μv), variable degree of amplification (200,000 - 500,000 times) is needed equal to the range of analog to digital convertor. The electrode impedance includes intrinsic impedance of the electrodes and the impedance of electrode-skin interface. For the measurement of any electrical activity say for example, the action potential generated in central nervous system, nerve or muscle must flow through the electrode into the amplifier and return to the patient through the ground lead. Electrode impedance results in drop of the amplitude of action potential.

This attenuated action potential reaches the amplifier. To reduce this attenuation, the impedance of the amplifier must be much greater than the electrode impedance. According to the recommended standards of the Guideline 9(A) the differential input impedance of the amplifier must be at least 100 mega ohms. This minimises the waveform distortion and improves noise rejection. Unequal electrode impedance imbalances

the electrode amplifier input, converting some of the noise into a differential signal, which is amplified to the same extent as the neurophysiological signal.

SIGNAL AVERAGER

The process of measuring the electrical activity in the brain in response to sound stimulus presented to the ear, is a very complicated and cumbersome process. This is so, because, some degree of random of random and spontaneous electrical activity is continuously occurring within the brain. A recording of this random electrical activity is called ELECTROENCEPHALOGRAPHY (EEG). The electrical activity set up in the brain, in response to a sound stimulus, mingles up and mixes with the random and spontaneous electrical activity occurring within the brain and gets obscured. The magnitude of the electrical activity evoked by a sound stimulus is only about 1/100 of that of spontaneous random electrical activity (which is also called 'Background potential'). To separate these two types of electrical activity, a process called 'signal averaging' is done. This is based on the fact that, evoked electrical activity is time specific and occur at a fixed point of time after the sound stimulation, whereas, the random electrical activity is not time specific and occur at random. Hence, if the electrical activity generated by a very

large number of separate sound stimuli at a specific point of time is added together, only the electrical activity evoked by the sound stimulus will keep on adding, whereas, the background potential occurring at random without any time specificity will cancel each other. Thus this signal averaging technique is used to clarify and not amplify the response and enables to get the uncontaminated measure of the sound evoked electrical activity.

A 10 millisecond epoch after the stimulus is generally averaged for BAEP studies. Atleast 1000 – 2000 trails are averaged to get a good quality recording. Two to three repetitions are done and done and superimposed to check for reproducibility. The latency values measured on the separate repetitions should agree with each other within 0.1 millisecond or less. The amplitude values should agree with each other within 10%.

DISPLAY

There are two techniques of display of waveforms namely

1. Analog Oscilloscope Display
2. Computer based digital video display

In Analog oscilloscope display neurophysiological signals are directly displayed on a cathode ray tube following amplification and filtering, advantage of which is that there is no limitation for dynamic high frequency response and it's an optimal means of displaying rapidly changing amplitude against time.

For digital display, Analog to Digital Converter (ADC) and digital processing technique are required and this is used in our apparatus NEUROSTIM. The analog to digital conversion is a process in which the continuously varying neurophysiological signal is sampled at discrete time intervals and the amplitude of signal is converted to a number following amplification and filtering. The unit of an ADC is a bit, which is a binary digit(0 or 1).

SENSITIVITY(GAIN) & SWEEP TIME

The latency and duration measurements of an action potential are influenced by the sensitivity and sweep time . On high sensitivity, the latency measurements are shorter. Increase in sweep speed results in shortening of latency.

ELECTRICAL SAFETY

In recording BERA, measures must be taken to assure the patient's safety. The grounding and the chassis leakage of all instruments connected to the patient or located in the same room as the patient must be must be periodically tested. Equipment should be designed to prevent inadvertent shock during power on, power – off and failures.

BAEP settings in our study

Apparatus **:** NEUROSTIM of Medicaid Systems

Electrical Montage **:** L: Cz – A1, R: Cz – A2 Ground: Fz

Amplifier **:** Low filter – 100 Hz High filter -3000 Hz

Analysis Time **:** 10 milliseconds

Number of EPOCHS **:** 2000 trails with two repetitions.

Nature of the stimulus to the test ear:

Broad band click of 100 micro seconds duration

Intensity – 80 dB

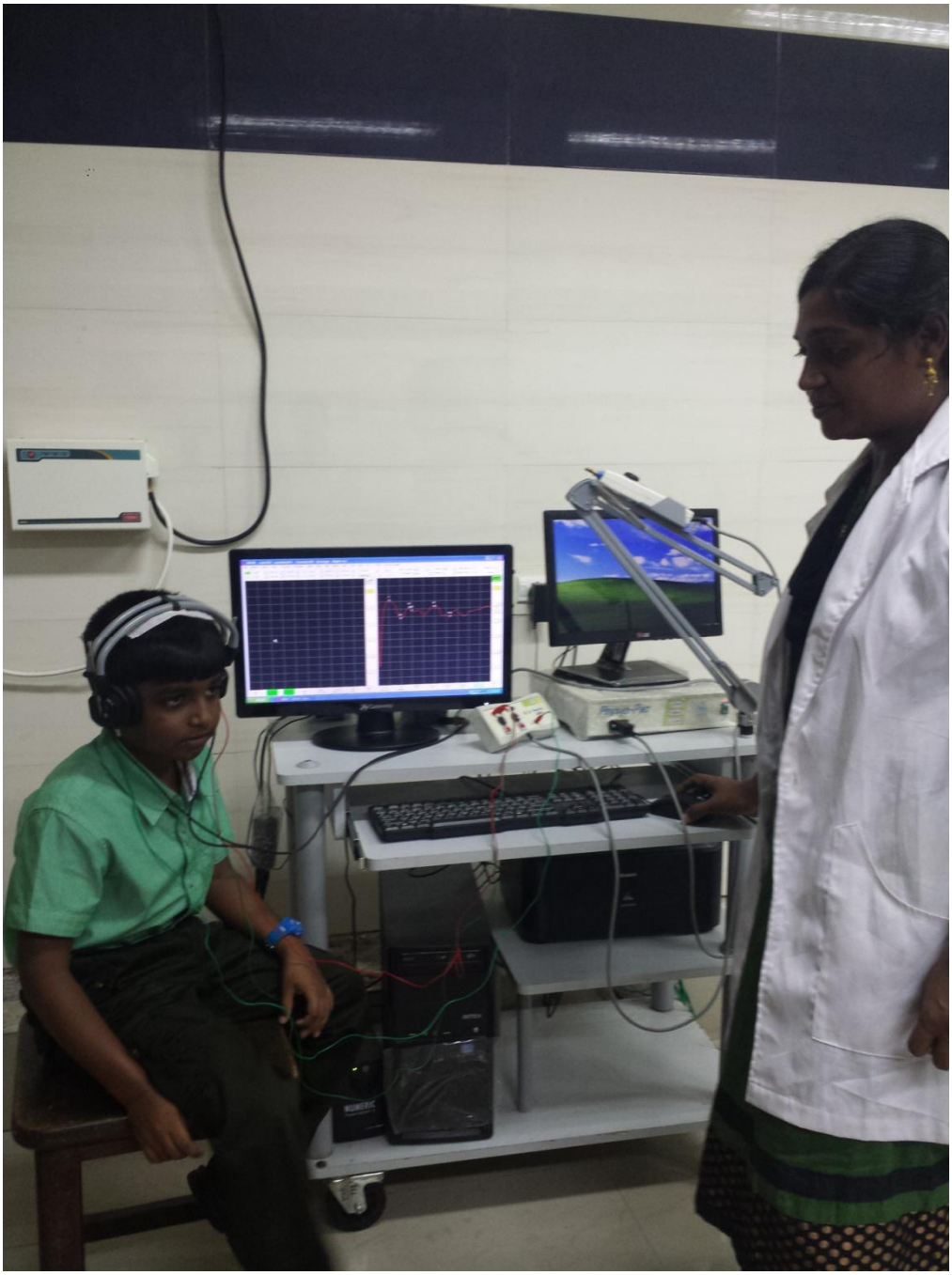
Stimulus rate – 11.1 clicks per second

Masking of Contra lateral ear:

By white noise of 50-60 dB is used.

PHOTO NO. 2

BAEP RECORDING IN A NORMAL CHILD



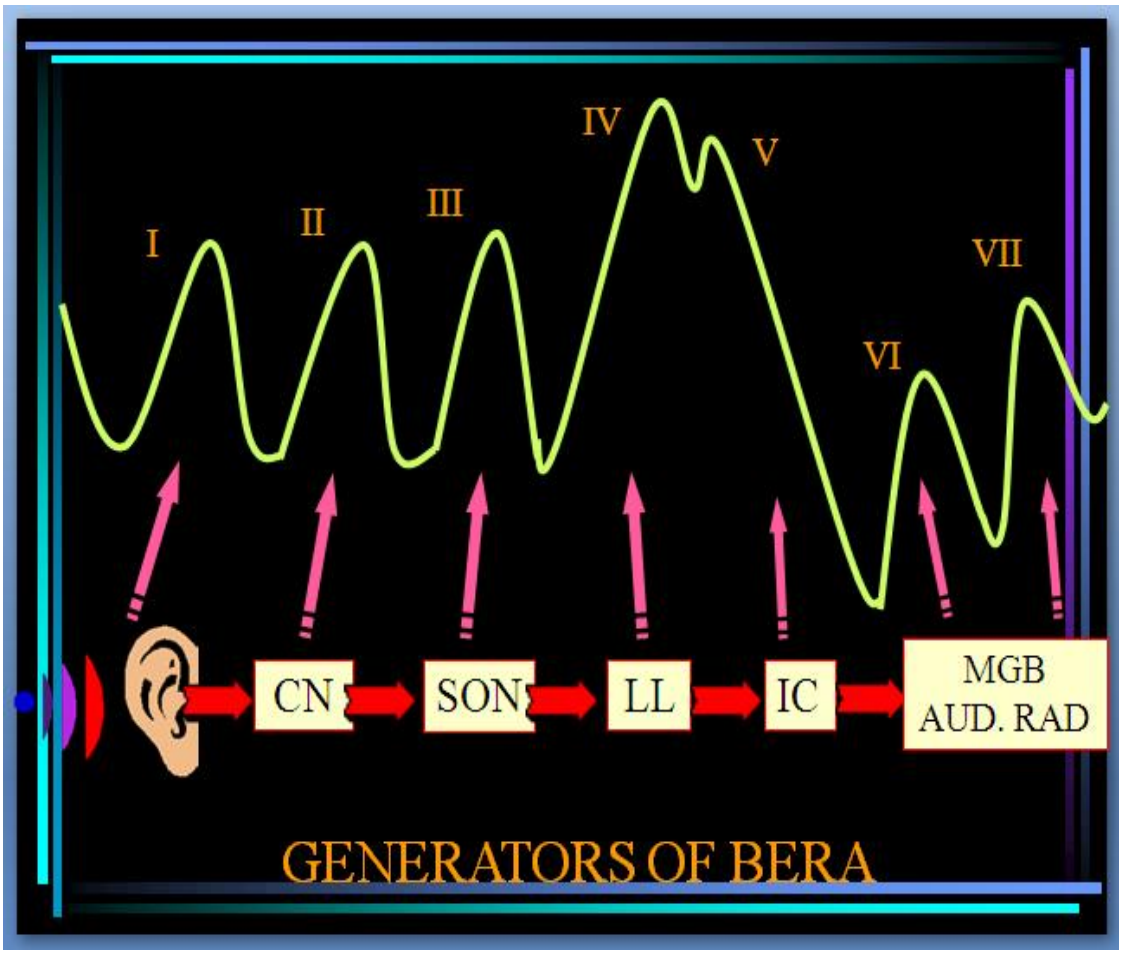
RECORDING PROCEDURE

The BAEPs were recorded from the scalp of each subject using a computerized EP recorder with gold plated disc electrodes placed according to the 10-20 international system and adjusting our EP recorder to the above specified settings. Active and ground electrodes are placed on the ipsilateral and contralateral mastoid processes respectively after cleaning the site with alcohol and application of EEG paste. The electrode on vertex acts as the reference. The skin-electrode impedance was kept below 5 ohms. The BAEP recording of each child was done in the presence of a parent.

NORMAL BAEP WAVEFORMS[99]

Auditory stimuli delivered to one or both ears evoke five to seven vertex positive waves in the human scalp, which appears about 10 milliseconds after the stimulus **(Picton et al, 1974)**[112]. These waves are named according to the sequence using roman numerals (I to VII) **(Chiappa et al, 1975)**[36]. The initial five peaks are of clinical interest.

FIGURE 8. GENERATORS OF BAEP WAVES



VIII N : Vestibulocochlear Nerve

CN : Cochlear nucleus

SON : Superior Olivary Nucleus

LL : Lateral Lemniscus

IC : Inferior Colliculus

MGB : Medial Geniculate Body

AUD RAD : Auditory Radiation

WAVE I

This is the initial upgoing peak in the ipsilateral recording channel just beyond the one millisecond mark on the BERA graph. It is generated from the auditory portion of the eighth cranial nerve, that is the proximal portion of the nerve lateral to the brainstem in contact with spiral ganglia. It is an important reference point for interpeak latency measurement **(Row MJ, 1978)**[123]. It appears 1.4 ms after the stimulus in normal subjects. Medial earlobe recording provides higher amplitude of wave I compared to mastoid recording **(Stockyard et al, 1979)**[148].This wave has to be recognised properly, because it gives us an idea whether the stimulus has crossed over from the cochlea and the distal end of auditory nerve, so that various BERA parameters of subsequent waveforms can be studied. If wave I is present, but wave II-V are absent, it suggests that the stimulus has reached the cochlea well enough, but is not being able to proceed further. If wave I is delayed (ie. Latency increased), but the interpeak latencies of I-II or I-V are normal, it indicates that either there is a conductive or cochlear pathology but once the impulse manage to cross the cochlea there is no subsequent obstruction, i.e. no retro-cochlear pathology. So, patients who have a CNS problem should have a preserved wave I, whereas those with peripheral hearing impairment may

have absent or poorly formed wave I, but relatively normal waves II – V **(Nuwer et al, 1994)**[107]. The wave I is a consistent BERA wave and is present in all normal subjects. Only marked peripheral lesions (cochlear or conductive pathology) abolish the waves.

WAVE II

It may be generated either at the cochlear nucleus or near the cochlear nucleus **(Row 111, 1978)**[123]. A portion of it may come from the auditory nerve fibres around the cochlear nucleus and this part of wave II may be preserved even in brainstem dead patients. Wave II may be poorly defined in neonates and some adults. It may sometimes appear as a small peak along the downgoing slope of wave I or may merge into the upgoing slope of wave III. This wave has a latency of approximately 2.8 millisec. And hence when it difficult to identify it should be looked for at or just before the 3ms mark of the BERA. It is more prominent and also has a prolonged latency on the contralateral recording channel compared to ipsilateral channel, sometimes fusing with wave III forming an M – shaped II-III complex **(Aminoff et al, 1994)**[8]

WAVE III

This wave probably originates from the lower pons as the impulse travels through the superior olivary nucleus and trapezoid body **(Row III, 1978)**[123].This wave precedes the wave IV. So, once the wave IV has been recognised wave III is identified as the upward peak between wave II and IV just beyond the 3ms mark on the graph. Wave III is usually a prominent peak and is followed by a prominent trough. In the contralateral channel wave III is smaller and appears earlier than in the ipsilateral channel because its amplitude is similar at the vertex and contralateral ear **(Goodin et al, 1994)**[54]. Sometimes the wave III is bifid and rarely it is fused with wave II. These are normal variants and has no clinical significance. In normal subjects the wave III is usually present at or around the 3.8ms mark on the BERA graph. The amplitude is of about .20 to .25 microvolts. The wave III is as consistent as I and V and in only about 1-2 % cases, the wave III may be absent in normal subjects.

WAVE IV

This wave is identified as the peak just preceding the wave V. So once wave V is identified, it not difficult to identify wave IV. Sometimes however wave IV and wave V become superimposed leading to

difficulties in identification of the waves. In such cases, it is worthwhile in using the contra- lateral ear as the reference. Other variations of wave IV are superimposition of wave V in the down slope i.e. descending arm of wave IV as also the superimposition of the small wave IV in the upstroke i.e. the ascending arm of wave V. These are normal variation and do not have clinical significance.

A distinct and separately identified wave IV is present in only 50-60% of subjects, in other cases the wave IV cannot be identified separately.

WAVE V

This wave ought to be identified before all of the other waves. It is the most reliable and easily identified wave in the BERA. The hallmark of the wave V is that there is a sharp negative (downward) deflection immediately following the peak. Hence ,when we find a peak beyond the 5ms mark on the graph which is followed by a long and sharp downward deflection dipping below the arbitrary horizontal line which bisects the other wave, one can identify it as wave V. Sometimes, however it is difficult to distinguish wave V from wave VI as the long sharp negative deflection atypically follows the peak of wave VI (instead of that of

wave V). However, in such confusion the clinician should ask for Cz-Ac recording of the BERA.Cz – Ac mean that the active recording electrode is on the vertex and the reference electrode is on the contra-lateral ear lobe .The wave V usually appears at 5.6 – 5.85 ms in normal subjects when the BERA test is done at 50 – 60 dB supra threshold level. Though the amplitude of the BERA waves is variable , yet it is usually the target and the most robust of the five BERA waves. It is always bigger than wave I and is usually nearly twice the size of wave I. Generators of wave IV&V probably lie in the upper pons or lower midbrain, lateral lemniscus and inferior colliculus. There are conflicting reports about ipsilateral or contralateral generation of waves IV & V but most of the evidences show a contralateral site of generation for wave V **(Starr et al, 1994)[144].**

WAVES VI & VII

They are not found in all normal subjects. They are generated in medial geniculate body and auditory radiation from the thalamus to temporal cortex respectively **(Row, 1980)[122]**

INTERPRETATION OF BAEP WAVEFORMS

The most constant and important waves are waves I, III & V **(Rosenhall et al.,1985)[121]**

The parameter of the Brainstem auditory evoked potentials that are studied are as follows.

a. Absolute latency and amplitude
b. Inter peak latencies (IPL)
c. Amplitude ratio of wave V / I complex
d. Inter ear inter peak differences.

The amplitude of the BAEP waveforms depends on the number of neurons activated by the auditory click stimulus and the level of synchronized activity of these neurons. The interpeaklatencies (IPLs) reflects conduction of the nerve impulse(AP) through the corresponding component of the auditory pathway **(Stockard JJ)** [147].

Absolute latency

Latency of a wave is the time interval between the onset of the stimulus and the peak of the wave measured in milliseconds. Absolute latencies are taken from the peak of the respective wave. The recommended method for latency comparison is to superimpose the major ascending and descending limbs of waves of two sides against a strong source of light. The absolute latency of the wave is most important for clinical measurement because it is most commonly present and easily identifiable.

Absolute amplitude

Amplitudes area not a very good criterion since amplitude of the wave is not as constant as latency of the waves. However amplitude measurements do yield some information which is used as supplementary evidence. Absolute amplitude are measured in microvolts from the peak of the wave to its trough. The absolute amplitudes are extremely variable in normal subjects **(Chiappa K.H)**[36].

INTER PEAK LATENCY (IPL)

Inter peak latency or inter wave latency is time interval between two different waves in the same ear. The clinical interpretation is based on IPLs **(Chiappa K.H)**[36]. The commonest IPLs used in clinical practice are :

I- V IPL

The latency difference between wave V and wave I is the measure of conduction from proximal VIII nerve through pons to mid brain. It is prolonged in various disorders such as demyelination, ischaemia and tumors which produce focal damage and degenerative disorders and hypoxia which produces diffuse damage **(Starr et al.,1994)**[144]. The upper limit of normal for I-V IPL is 4.5 msec. This IPL is slightly shorter in females and in older men. Normal right to left asymmetry should not

exceed 0.5ms. For full term infants this interval should be less than 5.4msec **(Goodin et al.,1994)**[54].

I- III IPL

The latency difference between wave III and I is a measure of conduction from VIII nerve across subarachnoid space into the core of the lower pons. This I-III IPL will be prolonged in lesions affecting the pontomedullary junction where the eighth nerve enters the brainstem or in the lower pons around superior olive or trapezoid body. Acoustic neuromas or other CP angle tumors can cause a delay at this juncture. Inflammation in subarachnoid space such as subarachnoid haemorrhage also can increase this interval **(Aminoff et al., 1994)**[8]**.** The upper limit of normal I-III IPL is about2.5 msec. Normal right-left asymmetry should not exceed 0.5 msec. An excessively long I-III IPL should not be considered unless there is associated prolongation of I-V IPL **(Matsuoka et al.,1994)**[94]

III – V IPL

III – V IPL is the measure of conduction from lower pons to mid brain. It is probably influenced by contra lateral conduction although contribution from ipsi lateral brain stem auditory pathways is also

suggested. Most of the evidences suggest contralateral brainstem site **(Nuwer et al.,1994)**[107]. The upper limit of normal III-V IPL is about 2.4 msec. Normal right-left asymmetry should not exceed 0.5 msec. An excessively long III-V IPL is not considered abnormal unless I-V interval or V/I amplitude ratio is also abnormal **(Goodin et al., 1994)**[54]

Amplitude ratio of wave V/I

The measurement commonly used in amplitude studies is amplitude related ratio, which is the ratio between the amplitude of two waves. Commonly the amplitude ratio of wave V/I is used clinically. Since the wave I is generated outside the CNS and wave V inside, these can be compared to determine the relationship of expected signal amplitude. It can be expressed either as percentage or ratio. The amplitude ratio should be between 50% and 300%. When the V/I amplitude ratio is less than 50% it suggests a small wave V and central hearing impairment. When the V/I amplitude ratio is greater than 300%, wave I is considered small and suggests peripheral hearing impairment such as high frequency or sensorineural hearing loss **(Aminoff et al.,1994)**[8].For full-term infants the lower limit of V/I is 30% **(Goodin et al.,1994)**[54].

Inter ear latency difference

It is the time interval difference between the two ears of the same wave. The difference in the absolute latency of a particular wave in between the two ears should not be more 0.5 ms, provided the same supra threshold sound stimulus has been presented to the two ears.

Table 2. NORMALWAVES OF BAEP

Waves(latency ms)	Chiappa et al1979	Misra and Kalita et al
I	1.7 ± 0.15	1.67 ± 0.17
II	2.8 ± 0.17	2.78 ± 0.21
III	3.9 ± 0.19	3.65 ± 0.22
IV	5.1 ± 0.24	5.0 ± 0.30
V	5.7 ± 0.25	5.72 ± 0.30
VI	7.3 ± 0.29	7.2 ± 0.48
I – III IPL	2.1 ± 0.15	1.99 ± 0.25
I – V IPL	4.0 ± 0.23	4.04 ± 0.25
III – V IPL	1.9 ± 0.18	2.08 ± 0.30

Terminologies used in evoked potential study(click stimulus intensity)

decibel (dB=1/10 Bel):

It is defined as ‘20 log (P1/P2)’, where P1 is the intensity of the sound to be measured and P2 is the intensity of the reference sound.

Sound pressure level (SPL):

It is the weakest sound heard by the most sensitive ear. It is the standard physical reference for sound (20 micropascals or 0.0002 dynes /cm2)

Hearing level (dBHL):

Zero dBHL corresponds to the average hearing threshold of a group of normal hearing young adults in a ideal listening environment.

Sensory level (dBSL):

This expresses the intensity of a sound as a function of the hearing threshold for an individual ear for any subject.

FACTORS AFFECTING BAEP RECORDING

TECHNICAL FACTORS

A. STIMULUS RATE

This is the number of clicks presented to the ear per second. The recommended rate is 10-40 clicks per second (In practice, the stimulus rate used is an odd figure like 11.1/sec). This is done to lessen the polluting effects of the 50 hertz noise from electrical circuits. If the stimulus rate is such that 50 which is divisible by it, the sound stimulus is

rejected. Very high stimulus rates, say, 80 or 100 clicks per second, change the latency and amplitude of the BAEP waves. Usually, the amplitude decreases and the latency increases if the stimulus rate is very high. Increase in click rate increases the absolute latencies and decreases the amplitude of most of the BAEP waveforms. IPLs increase slightly at higher rates **(Stockard et al.,1978&1979)**[146,147]. But **Chiappa et al.,1979** showed that increasing click rate from 10/s to 30/s has no value.

B. STIMULUS PHASE OR POLARITY

The phase or polarity of the click stimulus is one of the factors which can affect the latency, amplitude and even morphology of the BAEP waveforms. The phase of the click stimulus may be two types, viz. condensation phase and rarefaction phase. The transducer which produces the click sound has a diaphgram which vibrates i.e., moves outwards and inwards to produce the sound. When the diaphgram moves initially outwards i.e., towards the ear drum, the phase is called condensation phase. When the diaphragm of the transducers first move inwards, i.e., in a direction away from the ear drum, it is called rarefaction phase. For routine BAEP studies, use of the rarefaction phase is recommended because it produces better resolution of the BAEP waves. However, many neurologists use an alternating phase, that is,

rarefaction phase and the condensation phase alternating in close succession. This somewhat reduces the electrical and stimulus artifacts but at the same time reduces the sharpness of the BAEP wave peaks. The use of a condensation phase or even an alternating phase slightly increase the absolute latencies of the BERA waves I , II, III, IV (especially, if the patient has a frequency sensori- neural loss) as compared to that when a rarefaction phase is used. However the latency and amplitude of wave V is not much altered by the change in phase of sound stimulus.

C.INTENSITY OF THE SOUND STIMULUS

For routine BAEP studies, the intensity of the click stimulus of 60dB supra threshold is recommended, i.e., 60dB above the hearing threshold of the ear being tested. Some laboratories however perform the test at a slightly lower supra threshold, level say 40 or 50dB above threshold. Lowering the intensity of the click stimulus increases the absolute latencies and decreases the amplitude of the BERA waves. **Stockard et al., in 1978**[146] reported that absolute latencies increase and amplitudes diminish with decrease in intensity of click stimulus by abou 0.03 msec/dB. The first wave to be obscured by lowering the stimulus and intensity is usually wave I; wave V is the most stable and is the last wave to disappear when the stimulus intensity is gradually lowered. In

fact, the wave V is discernable even when the stimulus is just 10db above the behavioural threshold. Since the amplitude and latency of BAEP waves are dependent on the intensity of click sound for eliciting the Brainstem Auditory Evoked potentials, the neurotologist should always stick to using the same supra threshold stimulation not only in both ears of the same patient, but also in all patients such that the results are easily comparable. If the normal values of the latencies and amplitude in a particular laboratory has been setup, by using a 60dB supra threshold stimulation, then in all patients (in the laboratory) this 60dB supra threshold stimulus should essentially be used.

D. BINAURAL/MONOAURAL STIMULATION

In clinical studies only a monoaural stimulation is recommended because monoaural abnormalities are common in neurologic disease and in binaural stimulation response from normal ear may mask the abnormality of waveform in abnormal ear **(Stockard et al.,1978)**[146]. So that only one ear at a time should be tested. Presenting the sound stimulus to both ears together (binaural) increases the amplitude of the wave III, IV,V but not wave I.

E. FILTER CHARACTERS OF THE BAEP MACHINE

The BAEP machine should be so adjusted that it records only between a fixed range of frequencies. The lower limit of this frequency range, called lower frequency filter should be 100Hz or 150Hz and the higher limit called the high frequency filter should be either 3000 or 5000Hz. The high frequency is usually kept at 3000Hz. These are called filter settings and can be changed in the BAEP machine. Frequencies lower than 100Hz should be cut of such that EMG or EEG or other lower electrical noise is not able to contaminate the BAEP recording. Frequencies higher than 5000Hz should be cut off to reduce high frequency electrical noise artifacts.

To interpret the BAEP accurately and to compare with the normative data, the neurotologist should ensure that fixed or standard and correct filter settings have been used for BAEP recording. Altering the filter settings will change the amplitude ratios of the waves and introduce unwanted artifacts into the BAEP tracing.

F. NATURE OF SOUND USED

For eliciting the BAEP response, the sound stimulus used is a click sound as already mentioned. The click sounds are generated as square

wave pulses each of which are of 0.1 milliseconds of duration. When BAEP test is being done for neurological diagnosis, it is essential that all the BAEP waves are clearly recorded. Hence the sound stimuli (clicks only) are delivered at 50-60dB above hearing threshold since this evokes neat and robust easily recognizable wave peaks. When the BAEP is used for audiological purposes, sometimes pure tone sound stimulus (tone-pips) is used. With tone-pips, the BAEP wave morphology is poor and the sensitivity is also much lesser. With click evoked BAEP, the BAEP threshold (appearance of a recognizable wave V) is within 10dB of the hearing threshold whereas with tone-pips evoked BAEP, the BAEP threshold is 25-35dB above the behavioural hearing threshold.

With all these specifications, it is futile to compare the BAEP test done at 30dB supra threshold using an alternating phase and a stimulus rate of 81 Hz with that done at 60dB supra threshold with a rarefaction click phase and a stimulus rate of 11.1Hz.

NON TECHNICAL FACTORS

A. AGE OF THE PATIENT

In very young children, less than 2yrs of age, latencies are slightly prolonged even if the hearing is normal **(Starr et al.,1976)**[143]. BAEP

matures to adult pattern over a period from birth to the age of 18 – 24months **(Hecox andGalambos)**[51].The reason for this age related change is due to completion of myelination of the auditory neural pathway only by 2 yrs **(Tarantino et al .,1988)**[155]**.**There is an age related prolongation of latency of wave I but not of other waves like wave III which shows that ageing is a peripheral process. The IPL values especially III-V & I-V IPL which actually reflects the central conduction time does not show a significant change with increasing age **(Costa et al .,1990)**[40].In old age patients of more than 65yrs, some increase of latency of wave V is observed. Older adults have longer I-V IPL by 0.1-0.15 ms compared to younger individuals **(Nuwer et al.,1994)**[107]**.** Hence normative data for these special groups of population should be separately worked out.

B. GENDER OF THE PATIENT

The BAEPs show significant differences between males and females. Absolute latency of wave V and wave I-V IPL are consistently prolonged by 0.15 to 0.2 milliseconds for 60-70dbSL stimulation intensities. The amplitude of the BAEP is significant in females (upto 40-50%). These gender differences are seen in children only after 8yrs of age **(Stockard et al., 1978)**[146]. I – V IPL decreases by almost one second at

the time of menstrual periods. These differences between males and females are most probably related to the differences of their head size (corresponding to the thicker skulls and longer auditory pathway in males) and possibly also to their differences in core temperature, which tends to shorten IPL s.**(Taghavy A & Losslein H)**[152]

Table 3.Gender differences in normal BAEP waveforms

WAVES	Taghavy&Losslein et al 2006		Pedrialli et al 2004	
	Females	**Males**	**Females**	**Males**
I	1.59 ± 0.09	1.64 ± 0.16	1.44± 0.10	1.42 ± 0.06
II	2.75± 0.12	2.83 ± 0.19		
III	3.67 ± 0.15	3.91 ± 0.20	3.56 ± 0.09	3.61 ± 0.13
IV	4.97 ± 0.17	5.14 ± 0.25		
V	5.52 ± 0.15	5.80 ± 0.20	5.32 ± 0.13	5.54 ± 0.21
I –III	2.08 ± 0.13	2.27 ± 0.20	2.12 ± 0.11	2.18 ± 0.13
I – V	3.90 ± 0.19	4.18 ±0.24	3.88 ± 0.17	4.11 ± 0.21
III – V	1.85 ± 0.14	1.90 ± 0.19	1.75 ± 0.12	1.93± 0.14

C. TEMPERATURE

With decreasing central body temperature, the latencies of the BAEPs are increased **(Picton et al., 1982)**[112] **(Stockard JJ)**[147]. A 0.17 increase in wave V latency on 1^0 C reduction of body temperature is

reported. At 32.5^{0}C, BAEP waveforms are distinctly abnormal and at 27^{0}C the waveforms disappear.

D. HYPOGLYCEMIA

Hypoglycemia increases IPL I-V & III-V but changes in wave I latency was not significant **(Kern et al., 1994)**[73]

E. DRUGS

The BAEPs are resistant to the effect of drugs. A slight prolongation of wave V latency with barbiturates or alcohol is attributed to lowering of body temperature.

F. HEARING DISORDERS

In peripheral hearing disorders the absolute latencies of all waves are increased with no change in IPLs an effect similar to that of decreased stimulus intensity **(Chiappa K.H)**[36] **.**

G. OBESITY

Obesity prolongs absolute latencies of waves I, III and V but does not have any influence on interpeak latencies **(Aanandha Subramaniam K et al)**[1]**.**

H. HEIGHT

Height does not influence the parameters of BAEP waveforms.

PARAMETERS MEASURED IN BAEP

Amplitude and latencies of waves I, II,III, IV &V and I-III, I-V &III-V IPLs were measured.

ESTIMATION OF SERUM ZINC LEVELS

Under strict aseptic precautions, blood samples were collected by means of venepuncture and the separated serum was stored in deep freezer at 20^0C. Serum zinc levels were estimated in the Department of Biochemistry, Institute of Child Health, Egmore, Chennai.

PRINCIPLE

Zinc in an alkaline medium reacts with Nitro-PAPS to form a purple colored complex. Intensity of the color complex formed is directly proportional to the amount of Zinc present in the sample.

Zinc + Nitro-PAPS ======➔ Purple Colored Complex in Alkaline medium

Normal reference values : 60 – 120 micrograms / dl

PHOTO NO. 3

COLORIMETER AND SERUM SAMPLES

ZINC KIT

Contents of the kit : 75 ml of the kit contains 60 ml of Buffer Reagent(L1), 15 ml of Color Reagent(L2) and Zinc Standard(200 micrograms/dl)

Reagent Preparation

The color Reagent is poured into the bottle containing Buffer Reagent. This is the working reagent and is stable for 2 weeks when stored at 2-8^{0}C.

PROCEDURE

Wavelength / filter	:	570 nm / Yellow
Temperature	:	R. T.
Light Path	:	1 cm

Pipetting was done into clean dry test tubes labeled as Blank (B), Standard(S) and Test(T). 1 ml of working reagent and 0.05 ml of distilled water were added to test tube B, 1 ml of working reagent and 0.05 ml of zinc standard were added to test tube S and I ml of working reagent and 0.05 ml of serum sample were added to test tube T. The contents were mixed well and incubated at room temperature (25^{0}C) for 5 minutes. The absorbance of standard (Abs. S) & test sample(Abs. T) were measured against the Blank within 20 minutes.

CALCULATION

Zinc in micrograms / dl = Abs. T / Abs. S X 200

STATISTICAL ANALYSIS

Statistical analysis was done using the software SPSS version 21.

1. Student's T test was carried out to compare the means of variables between ADHD children and normal controls.

2. The analysis of variance was worked out to find out if there was significant differences in zinc levels and BAEP parameters among the three ADHD subtypes.

3. Pearson's correlation coefficient was carried out to find the correlations between the serum zinc levels and BAEP in ADHD children.

Results

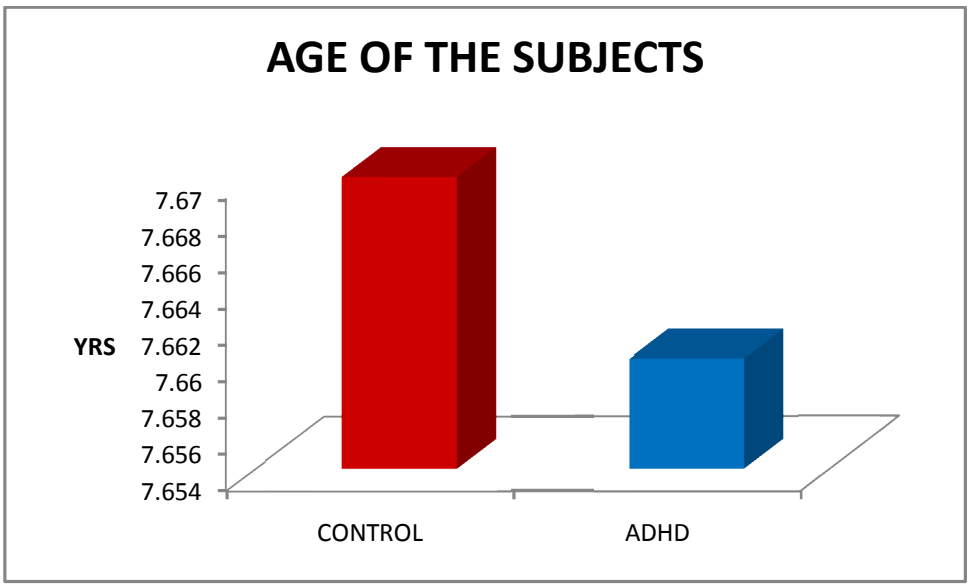
5. RESULTS

BAEP is an objective test to assess the functional integrity of auditory pathway and neurotransmission which is likely to be affected in ADHD children. In the present study various BAEP parameters and serum zinc levels are compared between the control group of children and ADHD children.

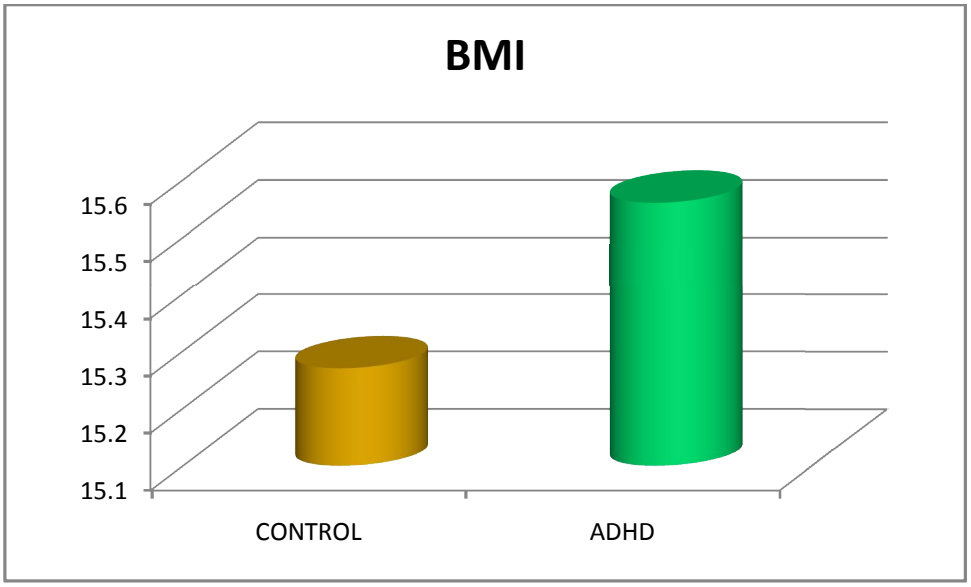
CHARACTERISTICS OF CONTROL AND STUDY GROUPS

The parameters used for selection of study and control subjects are furnished in Table 4. Among the children selected for the study, the mean age of the control children was 7.67±1.47 and the mean age for ADHD group was 7.66±1.52 both in within the range of 6 to 11 years. Among the ADHD children selected 10 belong to the combined type of ADHD and 10 each to the inattentive and hyperactive subgroups. The mean height of control children was 123.18±7.5 and that of ADHD children was 124.7±8.06. The mean weight for control children was 23.37±4.15 while that of ADHD group was 24.38±4.33. The average BMI for control children was 15.27±0.82 and that of ADHD group was 15.56±0.90. Thus there was no significant difference between the control and ADHD group

Graph 1. Comparison of Age between control and ADHD children



Graph 2.Comparison of BMI between control and ADHD children



in terms of height, weight and BMI making the two groups well comparable.

BMI was calculated using the formula weight in kg/height in cm^2 and BMI percentile was compared between normal healthy children of same age and sex.

BMI between 5^{th} and 85^{th} percentile is normal.

BMI between 85^{th} and 95^{th} percentile is overweight.

BMI < 5^{th} percentile is underweight.

BMI > 95^{th} percentile is obese.

The specific ENT examination which include examination of the auditory canal for wax and assessment of hearing ability by pure-tone audiometry was normal in both control and ADHD children.

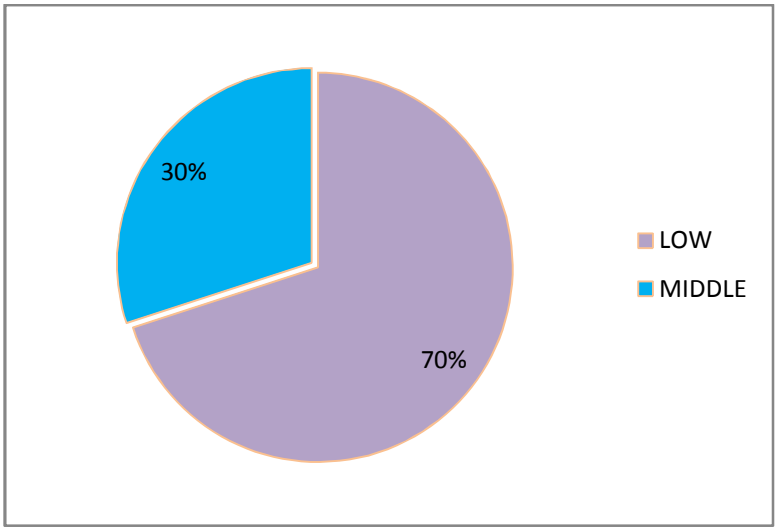
Table 4. Comparison of parameters (Mean ±SD) between control and ADHD children

Sl. No	Variables	Normal children	ADHD children	P value
1.	Age (years)	7.67 ± 1.47	7.66 ± 1.52	0.97
2.	Weight (kg)	23.37 ± 4.15	24.38 ± 4.33	0.36
3.	Height (cms)	123.18 ± 7.5	124.7 ± 8.06	0.45
4.	BMI	15.27 ± 0.82	15.56 ± 0.90	0.19
5.	ENT Examination	Normal	Normal	

SOCIO-ECONOMIC PROFILE

Twenty-one out of the thirty ADHD children belonged to low socioeconomic group whereas the remaining nine children belonged to the middle class. Thus the prevalence of ADHD was found to be high in the lower socioeconomic group accounting to be about 70%.

Graph 3. Distribution of ADHD children among different socio-economic classes



The random selection of ADHD children during the study period has given a prevalence of about 70% is concordant with the study conducted by **Malhi P et al**[91] and several other studies.

BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP) VARIABLES

The variables pertaining to BAEP between normal and ADHD children are furnished in Tables 5 - 8.

Table 5. Mean ± SD of Absolute wave latencies between normal and ADHD children (RIGHT EAR)

WAVE	NORMAL	ADHD	T TEST	P VALUE
I	1.5 ± 0.06	1.49 ± 0.06	0.65	0.52
III	3.54 ± 0.18	3.67 ± 0.23	2.44	0.02
V	5.39 ± 0.17	5.49 ± 0.19	2.29	0.02

wave III (p = 0.02) : significant; wave V (p = 0.02) : significant

wave I (p = 0.52) : not significant.

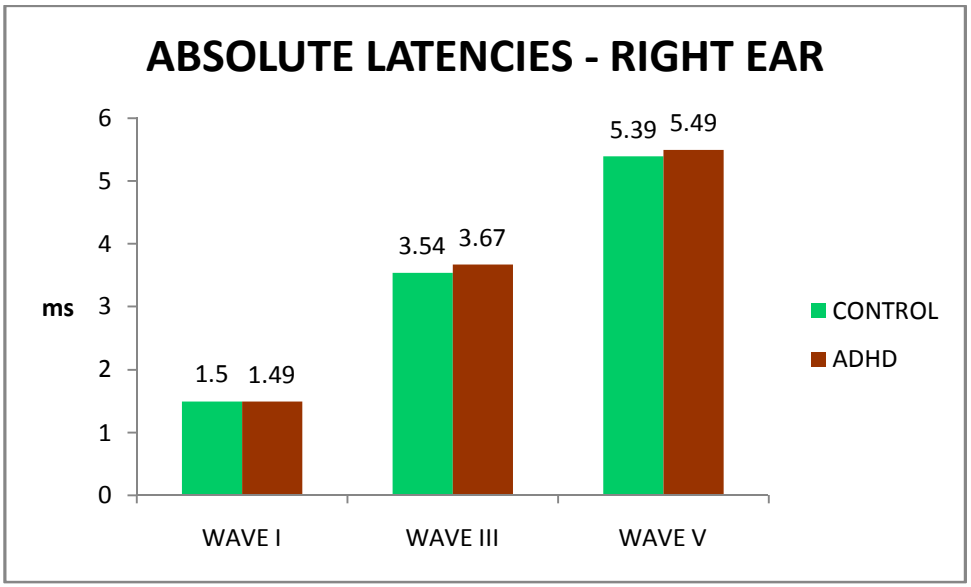
Table 6. Mean ± SD of Interpeak latencies (IPLs) between normal and ADHD children (RIGHT EAR).

IPL	NORMAL	ADHD	T VALUE	P VALUE
I – III	2.039 ± 0.19	2.18 ± 0.25	2.46	0.01
I – V	3.89 ± 0.18	4.01 ± 0.22	2.31	0.02
III – V	1.85 ± 0.09	1.83 ± 0.23	0.38	0.70

IPL I – III (p = 0.01) : significant ; IPL I – V (p = 0.02) : significant ;

IPL III – V (p = 0.70) : not significant.

Graph 4. Comparison of Absolute latencies of Right ear between normal and ADHD children



Graph 5. Comparison of Interpeak latencies of Right ear between normal and ADHD children

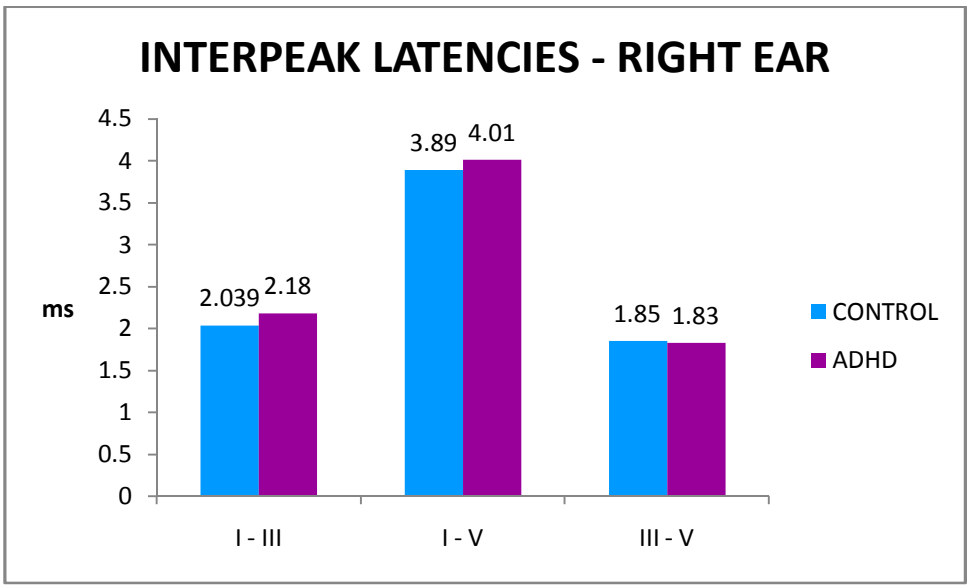


Table 7. Mean ± SD of Absolute wave latencies between normal and ADHD children (LEFT EAR).

WAVE	NORMAL	ADHD	T VALUE	P VALUE
I	1.34 ± 0.32	1.44 ± 0.16	1.52	0.13
III	3.43 ± 0.27	3.67 ± 0.29	3.31	0.01
V	5.35 ± 0.32	5.55 ± 0.40	2.09	0.04

wave III ($p = 0.01$) : significant ; wave V ($p = 0.04$) : significant ;

wave I ($p = 0.13$) : not significant.

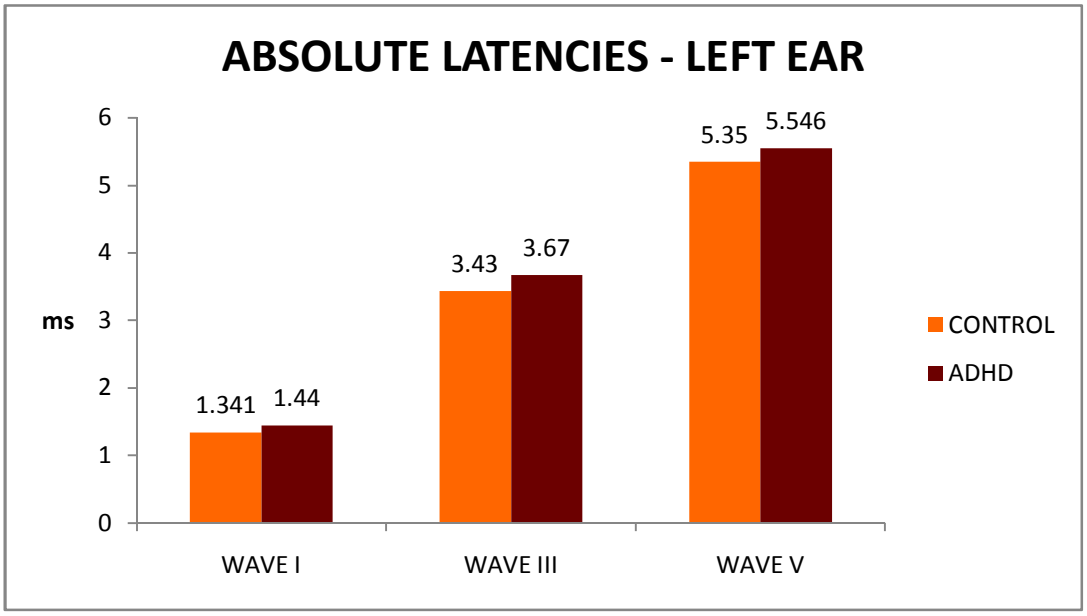
Table 8. Mean ± SD of Interpeak latencies(IPLs) between normal and ADHD children (LEFT EAR).

IPL(ms)	NORMAL	ADHD	T VALUE	P VALUE
I – III	2.09 ± 0.49	2.23 ±0.33	59.30	0.20
I – V	4.01 ± 0.39	4.10 ± 0.45	0.80	0.42
III – V	1.92 ± 0.42	1.87 ± 0.36	0.41	0.68

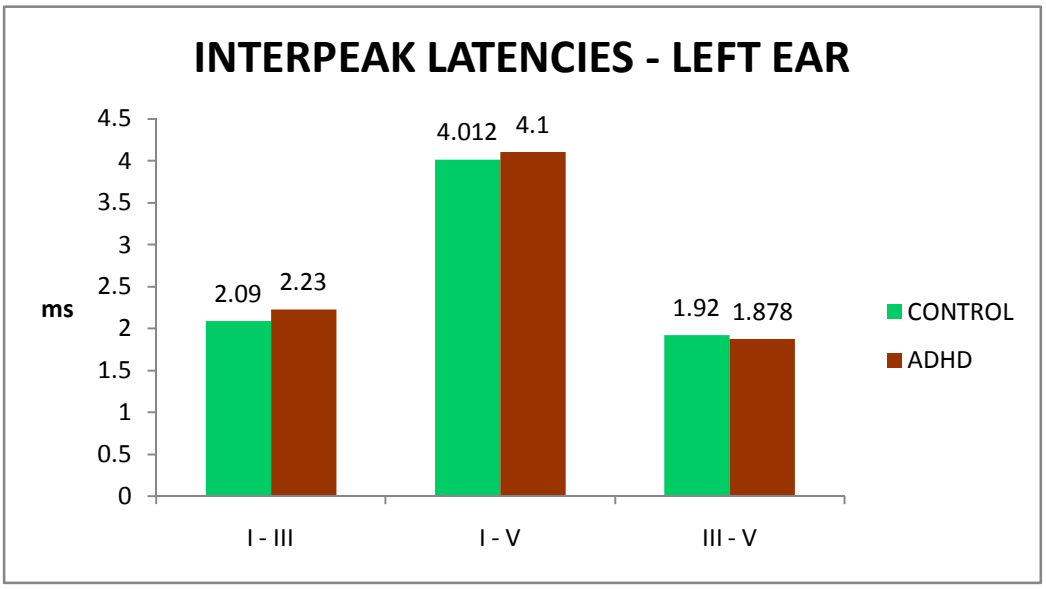
I – III IPL ($p = 0.20$) : not significant; I – V IPL ($p = 0.42$) : not significant;

III – V IPL ($p = 0.68$) : not significant.

Graph 6. Comparison of absolute latencies of Left ear between normal and ADHD children



Graph 7. Comparison of Interpeak latencies of Left ear between normal and ADHD children



SERUM ZINC LEVELS

The difference in the mean values of serum zinc levels between normal and ADHD children are given in Table 9.

Table 9. Mean ± SD of Serum Zinc levels between normal and ADHD children.

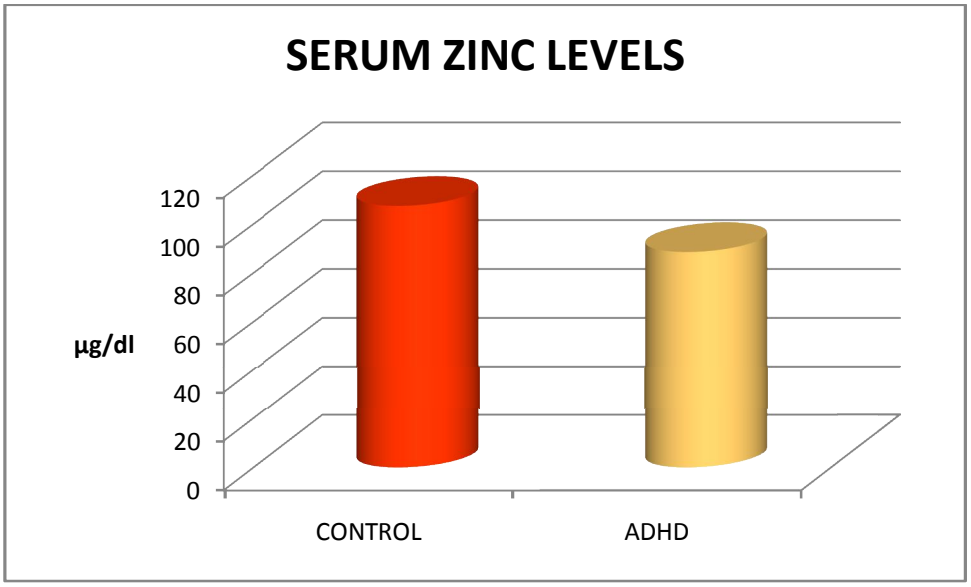
GROUPS	SERUM ZINC LEVELS(µg/dl)	T VALUE	P VALUE
NORMAL	107.27 ± 28.13	2.53	0.01
ADHD	88.4 ± 29.55		

P value : 0.01 (significant)

Analysis of Variance of Serum Zinc levels and BAEP variables among three ADHD subtypes

Analysis of Variance was done for serum zinc levels and various BAEP variables among the three ADHD subtypes namely predominantly inattentive, combined and hyperactive-impulsive types. Significant variation was found for serum zinc levels among the three subtypes of ADHD whereas no significance was attached to difference in BAEP

Graph 8.Comparison of Serum zinc levels between normal and ADHD children



variables among these three subtypes. The results of the analysis of variance are furnished in the Tables 10 &11.

Table 10.ANOVA for serum zinc levels among the three ADHD subtypes

Source of variation	Sum of squares	df	Mean square	F statistics
Between groups	7133.6	2	3566.8	5.29541
Within groups	18186.2	27	673.56	

P value = 0.01 (significant)

Table 11.ANOVA for IPL I – III of RIGHT EAR among three ADHD subtypes

Source of variation	Sum of squares	df	Mean square	F statistics
Between groups	0.10374	2	0.05187	0.8494
Within groups	1.6488	27	0.06107	

P value = 0.44 (not significant)

Analysis of variance among three ADHD subtypes were not significant for absolute nor interpeak latencies of right and left ear.

Correlation of BAEP variables with serum zinc levels

Various BAEP variables were correlated with serum zinc levels using Pearson's correlation coefficient and the results are furnished in Tables 12 and 13. Correlation of serum zinc levels with BAEP variables showed a weak positive correlation on both right and left ears which is not significant.

Table 12.Correlation of BAEP variables of right ear with serum zinc levels

BAEP VARIABLES		SERUM ZINC LEVELS
WAVE III	r	0.138
	P	0.466
IPL I – III	r	0.188
	P	0.321
WAVE V	r	0.016
	P	0.932
IPL I – V	r	0.084
	P	0.658

Table 13.Correlation of BAEP variables of left ear with serum zinc levels

BAEP VARIABLES		SERUM ZINC LEVELS
WAVE III	r	0.158
	p	0.405
IPL I – III	r	0.255
	p	0.174
WAVE V	r	0.199
	p	0.293
IPL I – V	r	0.258
	p	0.168

Discussion

6. DISCUSSION

All the ADHD children included in the present study had fulfilled the DSM IV criteria and Brainstem Auditory Evoked Potentials were recorded and the results were evaluated for assessing the central auditory processing and functional integrity of auditory pathway.

CHARACTERISTICS OF STUDY SUBJECTS

The mean age of ADHD children included in the present study was 7.665 ± 1.52 years who were in the range of 6 – 11 years.

This is in accordance with the mean age of ADHD children in the study done by **Hannan Azzam et al** [56] (7.4 ±2yrs). The average age of ADHD children in the study conducted by **A Puente et al**[2] was about 9 yrs whereas the average age of control group was 22 yrs and this may provoke a doubt about the prolongation of the absolute and interpeak latencies as due the differences in age among the controls and ADHD children. But in the present study there was no significant age differences among the control and ADHD group and therefore, it can be inferred that the changes in the BAEP waveforms which are evidences of defects in the central auditory processing and functional integrity of auditory

pathways in the ADHD children are perse due to the disorder rather than due to age related changes. **Aanandha Subramaniam K et al**[1] have shown that obesity prolongs the absolute latencies of waves I, III and V and since in the present study the height, weight and BMI of the ADHD children were within the normal range (between 5th percentile and 85th percentile) and also as there was no significant differences among control and ADHD children, it could be inferred that the changes in the absolute latencies of both ears are due to ADHD rather than BMI related changes.

BRAINSTEM AUDITORY EVOKED POTENTIAL

The present study deals with the changes in BAEP due to Attention Deficit Hyperactivity Disorder. **A Puente et al** [2] have shown that there is defective central auditory processing and asymmetric conduction of auditory stimuli in ADHD. Hence ADHD children with associated specific learning disability (SLD), autism and other neurological disorders who may also have defective auditory processing were excluded from the study. The main parameters that were considered for detecting abnormal auditory processing were absolute wave latencies and interpeak latencies.

WAVE I

The mean values of wave I in ADHD children were 1.49± 0.06 and 1.44 ± 0.16 milliseconds respectively in right and left ears. There is no significant difference (p = 0.52 and 0.14 in right and left ears respectively) from the latency of wave I recorded in normal children (1.5 ±0.06 and 1.34 ± 0.32 respectively). This is consistent with the study conducted by **Hannan Azzam et al[56]** in which there was no significant difference in absolute latencies of wave I between ADHD and control groups(1.4 ± 0.1 and 1.4 ± o.1; p value : 0.6 in right ear & 1.3 ± 0.1 and 1.4 ± 0.1 ; p value :0.2 in left ear) in ADHD and control children respectively. Similar findings were also recorded in studies conducted by **Neelam Vaney et al[105], A Puente et al [2] and Lahat et al[79].** If wave I is delayed , it indicates that there is a cochlear pathology and since in the present study as there is no significant prolongation of wave I latency of ADHD children when compared to normal children we can infer that there is no cochlear i.e; peripheral pathology in ADHD children.

WAVES III AND V

The mean values recorded in ADHD children were 3.67 ± 0.23 and 3.67 ± 0.29 for wave III in right and left ears respectively and 5.497 ±

0.19 and 5.546 ± 0.40 for wave V in right and left ears respectively. These values were significantly higher than those recorded in controls. This is consistent with the study conducted by **Hannan Azzam et al**[56] who showed statistically significant prolongation of wave III and V latencies in ADHD children.

A Puente et al[2] showed prolonged latencies of waves III and V in children with ADHD**. Lahat et al**[79] showed prolonged wave V latency in males and wave III and wave V latencies in females. The present study was conducted only considering ADHD boys and so the above findings of any difference among genders could not be shown**. Neelam Vaney et al**[105] has shown that there was no statistically significant prolongation of wave III and V latencies in ADHD children. Though not statistically significant there was a minimal prolongation of wave III and V latencies in ADHD children when compared to controls.

INTERPEAK LATENCIES I – III and I – V

The mean values of I – III IPL were 2.18 ± 0.25 and 2.23 ± 0.33 and I – V IPL were 4.01 ± 0.22 and 4.10 ± 0.45 in right and left ears respectively of ADHD children. These were statistically significant in right ear (p value 0.01for IPL I-III and 0.02 for I-V IPL) but was not

statistically significant in left ear (p value 0.20 for IPL I-III and 0.42 for I-V IPL). Though not statistically significant, there was a mild prolongation of I-III and I-V IPLs in left ear.

Hannan Azzam et al[56] found statistically significant differences in both I-III and I-V IPLs in both right and left ears (I-III IPL 2.1±0.2 and 2.2±0.2 and I-V IPL 4±0.3 and 3.8±0.4 in right and left ears respectively. The reason for the absence of significant prolongation in the left ear in the present study may be due to asymmetric conduction of auditory stimuli in both the ears.

A Puente et al[2] showed prolonged I-III and I-V IPLs in ADHD children compared to controls. **Lahat et al**[79] showed significant prolongation of both I-III and I-V IPLs in females whereas ADHD boys had prolongation of I-V IPL alone.

The statistically significant prolongation of the absolute latencies III and V as well as interpeak latencies I-III and I-V suggest synaptic delay due to abnormal brainstem neurotransmission and defect in central auditory processing which leads to the disruption of functional integrity of the auditory pathways.

In contrast , **Neelam Vaney et al**[105] showed that there was no significant prolongation of I-III or I-V IPL in ADHD children compared to controls. Though not statistically significant, however there was a mild prolongation of both I-III and I-V IPLs in ADHD children compared to controls. The reason for this contrasting finding may be due to the difference in size of sample in the contrasting study than in the present study and also due to the variation in the type of study subjects selected. The type of ADHD involved in the contrasting study was of combined type where as in the present study 10 each from the three subtypes of ADHD were selected. Preterm children were excluded from the contrasting study whereas they were included in the present study. The other reasons may be due to variation in standardization of the equipment and BAEP settings used. In the present study, 2000 click stimuli were delivered at the rate of 11.1 Hz at 80 dB whereas in the contrasting study 1000 click stimuli were delivered at the rate of 10 Hz 60 dB above the hearing threshold. One another reason could be the method of analysis. The averages for right and left ear were taken and analyzed in the contrasting study whereas the right and left ears were analyzed separately in the present study and also in the study which is in agreement with the present study **(Hannan Azzam**[56] **et al).**

III – V IPL

There is no statistically significant difference in III-V IPL of both ears in ADHD children compared to normal children (p values 0.70 and 0.67 in right and left ears) of ADHD children respectively. This is in accordance with similar studies **(Hannan Azzam [56]et al , A Puente[2] et al, Lahat [79] et al and Neelam Vaney [105] et al).**

The prolongation in absolute latencies of waves III and V and IPLs I-III and I-V suggest an objective evidence of subclinical defect in central auditory processing. The underlying defect may be due to variation in the synaptic function, axonal growth and myelination. Normal perception requires appropriate timing of stimulus encoded in the auditory brainstem structures. Prolonged latencies of the above waves suggest delay in the appropriate timing of the stimulus in reaching the auditory brainstem structures. A defect in the auditory processing of sequential information is also reported among these children. Though the present study throws light onto auditory conduction abnormality as a factor contributing to the attention deficit, further studies involving larger samples of subjects may provide better elucidation and strengthening of the above facts shown in the present study.

SERUM ZINC LEVELS

The serum levels of zinc were significantly lower in ADHD children (p value 0.01) with the mean values of 88.4 ± 29.55µg/dl when compared to the controls with mean values of 107.27 ± 28.13µg/dl. This is consistent with several other similar studies which has shown lower serum zinc levels in ADHD children compared to controls.

Kozielec [76] et al in a study among ADHD children in Poland showed that serum zinc levels were significantly lower in ADHD children($p < 0.001$) when compared to controls.

Toren [161] et al in Israel had reported significantly lower serum zinc levels in a group of 39 boys and 4 girls with ADHD in the age group of 6-16 years compared to 28 age matched controls. This age group is nearly similar to age of the ADHD children in the present study.

Bekaroglu[20] et al in Turkey recorded low mean serum zinc levels in ADHD children(60.6 ± 9.9µg/dl when compared to controls(105.8 ± 13.2µg/dl).

Starobrat-Hermelin[142] et al in Poland reported iron, copper, magnesium and calcium deficiencies in addition to zinc deficiency by analyzing serum, red blood cells and hair of ADHD children.

Bettger [22] et al has shown that zinc is essential for maintaining the neuronal structure as it is essential for the metabolism of PUFA which are the building blocks of neuronal membranes by acting as a cofactor for the enzyme delta-6-desaturase. **Toren [161] et al** has shown that zinc is a cofactor for metabolism of dopamine which is involved in the pathogenesis of ADHD and so may contribute to the abnormal central auditory processing in ADHD by affecting appropriate neurotransmission. The main defect in ADHD may be in myelination of neurons, neuronal growth and abnormal neurotransmission the pathogenesis of which may be contributed by zinc deficiency in ADHD children found in the present study.

Analysis of variance among the three ADHD subtypes showed significant differences(p value 0.01) among the inattentive, hyperactive-impulsive and combined subtypes of ADHD in terms of serum zinc levels.

Arnold [12] et al 2005 in an American study reported that low serum zinc levels negatively correlated (Sr = -45 and p = 0.004) with parent and teacher rated inattention but not with hyperactivity and impulsivity. But another study by **Bilici et al[28]** in turkey showed that low serum zinc levels correlated with hyperactivity but not with inattention.

Analysis of variance among the three ADHD subtypes did not show significant variation in terms of BAEP waveforms.

CORRELATION OF BAEP VARIABLES

There was no significant correlation between serum zinc levels and various BAEP parameters of ADHD children. All the BAEP parameters showed weak positive correlation with serum zinc levels. But there should be negative correlation as ADHD children will have low serum zinc levels which leads to prolonged absolute and interpeak latencies of BAEP waveforms as zinc contributes to the effective neurotransmission due to its cofactor role in the metabolism of dopamine implicated in the pathogenesis of ADHD and also it is implicated in the metabolism of PUFA which are the building blocks of neuronal membranes.

The reasons for the contradictory weak positive correlation between serum zinc levels and BAEP waveforms in the present study may be attributed to the minimum sample size and variations among the ADHD children.

Conclusion

7. CONCLUSION

It has been suggested that asymmetrical auditory stimuli conduction in the brainstem auditory structures plays a role in the pathogenesis of ADHD and in the present study the above fact is proved beyond doubt by the prolongation of various absolute latencies and interpeak latencies of the BAEP waves.

The absolute latency of waveform points out to time of conduction of auditory stimulus along the various components of auditory pathway and interpeak latencies show neuronal conduction in segments of auditory pathway.

Decreased serum zinc levels are seen in children with ADHD. Zinc contributes to effective neurotransmission in the auditory pathway by acting as a cofactor for dopamine involved in the pathogenesis of ADHD. It also acts as building blocks of neuronal membranes as it is involved in the metabolism of PUFAs which constitute important components of neuronal membranes. So zinc supplementation may benefit ADHD children by correcting the altered neurotransmission which could be evaluated by BAEP study, which is a non-invasive neurophysiological tool which provides useful information about the central auditory processing. Further studies are recommended to elucidate and strengthen the above facts.

Summary

8. SUMMARY

The present study was conducted to evaluate the functional integrity of auditory pathway and central auditory processing by Brainstem Auditory Evoked Potentials and to determine the variation of serum zinc levels and BAEP waveforms among the three ADHD subtypes.

30 ADHD children, 10 each from each of the three ADHD subtypes and 30 normal children were included in the study and BAEPs were recorded. Most of the ADHD children showed prolonged absolute latencies of waves III and V and IPLs I – III and I – V when compared to age and BMI matched controls. Thus the results indicate that there is a defective central auditory processing in ADHD.

Decreased serum zinc levels were seen in ADHD children compared to controls and this indicates the role of zinc in the pathogenesis of ADHD. Analysis of variance for serum zinc levels among the three subtypes show that there are significant differences among the three groups in zinc levels.

With the above results, it is proved that central auditory processing is defective in ADHD and zinc supplementation may be beneficial in ADHD children

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Annexures

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax: 044 25363970

CERTIFICATE OF APPROVAL

To

Dr.J.Anitha Ponmalar,
Postgraduate
Institute of Physiology and Experimental Medicine,
Madras Medical College, Chennai-3.

Dear **Dr. J.Anitha Ponmalar,**

The Institutional Ethics Committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled **"Evaluation of Brainstem auditory evoked potential and serum Zinc levels in children with Attention Deficit Hyperactivity Disorder"** No.05042014.

The following members of Ethics Committee were present in the meeting held on 11.03.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C.Rajendran, M.D,	-- Chairperson
2.	Prof. Kalaiselvi, M.D, Vice Principal, MMC, Ch-3	-- Member Secretary
3.	Prof. Nandhini, M.D, Inst. of Pharmacology, MMC, Ch-3	-- Member
4.	Prof.Bhavani Sankar, M.S, Prof & HOD General Surgery, MMC, Ch-3	-- Member
5.	Prof.V.Padmavathi, M.D, I/c. Director of Pathology, MMC, Ch-3	-- Member
6.	Thiru. S. Govindasamy, BA., BL	-- Lawyer
7.	Tmt.Arnold Saulina, MA MSW	-- Social Scientist
8.	Thiru.S.Ramesh Kumar, Administrative Officer, MMC, Ch-3.	-- Lay Person

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

21/4/14

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

21.04.14

INFORMED CONSENT FORM

Title of the study: "Evaluation of Brainstem auditory evoked potential and serum zinc levels in children with Attention Deficit Hyperactivity Disorder"

Name of the Participant:

Name of the Principal Investigator: DR.J.Anitha Ponmalar

Name of the Institution:

Institute of Physiology and Experimental Medicine,

Madras Medical College and Institute of Child Health,

Egmore, Chennai-8.

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am the guardian of the child and, exercising my free power of choice, hereby give my consent for my child to be included as a participant in **"Evaluation of Brainstem Auditory Evoked Potential and serum Zinc levels in children with Attention Deficit Hyperactivity Disorder"**

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my child's rights and responsibilities by the investigator.
5. I have informed the investigator of all the treatments my child is taking or have taken in the past _____ months including any native (alternative) treatment.

6. I have been advised about the risks associated with my child's participation in this study.

7. I agree to cooperate with the investigator and I will inform him/her immediately if my child suffers unusual symptoms.

8. My child has not participated in any research study within the past _____month(s).

9. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my child's future treatment in this hospital.

10. I am also aware that the investigator may terminate my child's participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from my child as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understood that my child's identity will be kept confidential if my data are publicly presented.

14. I have had my questions answered to my satisfaction.

15. I have decided my child to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

INFORMATION TO PARTICIPANTS

Investigator: DR.J.Anitha Ponmalar

Name of Participant:

Title:

Your child is invited to take part in this research/ study /procedures. The information in this document is meant to help you decide whether or not your child to take part. Please feel free to ask if you have any queries or concerns.

Your child is asked to participate in this study being conducted in

Institute of Physiology and Experimental Medicine,
Madras Medical College and Institute of Child Health,
Egmore, Chennai – 8.

What is the Purpose of the Research?

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders of childhood with a prevalence rate of 5-8%. Three subtypes have been identified in the Diagnostic and Statistical Manual (DSM-1V) according to the constituent symptom profiles of inattention and hyperactivity/impulsivity. The combined subtype is the most prevalent (61%) compared to inattentive (30%) and hyperactive type(9%).Defects in midbrain dopamine systems were recently implicated in the pathogenesis of ADHD.Convergent data from neuroimaging, neuropsychology and neurochemical studies pointed out involvement of frontostriatal network as a likely contributor to pathophysiology of ADHD. ADHD is characterised by the impact of abnormal signals carried by midbrain dopamine system on frontal brain areas that implement cognitive control.

The Study Design

Thirty children with ADHD will be selected for the study.

Study Procedures

The study involves assessment of Brainstem auditory evoked potential and serum zinc levels.

Your child will be required to visit the hospital once during the study.

5ml of blood will be collected simultaneously during the study. Blood collection

Involves prick with a needle and syringe.

In addition, if you notice any physical or mental changes in your child , you must contact the persons listed at the end of the document.

Your child may have to come to the hospital (study site) for examination and investigations apart from the scheduled visits, if required.

Possible Risks to your child - Nil

Possible benefits to your child- Zinc deficiency and hearing disability if present can be diagnosed at an early stage so that proper intervention can be taken.

Possible benefits to other people

The result of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefits to future patients.

Confidentiality of the information obtained from your child

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, IEC and any person or agency required by law like the Drug Controller General of India to view your child's data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decisions to not to participate in this research study will not affect your child's medical care or your relationship with investigator or the institution. Your doctor will still take care of your child and your child will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during course of the study without giving any reasons.

However, it is advisable that you talk to the research team prior to stopping the treatment.

PROFORMA

1. Name :
2. Age:
3. Sex:
4. Address :
5. Complaints/duration:
6. History of present illness:
7. History of any hearing problem ?
8. Past history:
9. History of any drug intake
10. History of associated illness:
11. Developmental history:
12. Family History of ADHD or other psychiatric illness

CLINICAL EXAMINATION

General examination:

Vitals:

Pulse rate:

Respiratory rate:

Anthropometry:

Ht :

Wt :

Systemic examination:

Cardiovascular system:

Respiratory system:

Gastrointestinal system:

Central nervous system:

ENT Examination :

Examination of external ear

Otoscopic examination

Tuning fork tests

Pure tone Audiometry

IQ Assessment

Serum Zinc levels

Master Chart

MASTER CHART FOR CONTROL CHILDREN

					LATENCY RT EAR (ms)						LATENCY LT EAR (ms)						µg/dl
SL NO	AGE	WT	HT	BMI	WAVE I	WAVE III	WAVE V	IPL I-III	IPL I-V	IPL III-V	WAVE I	WAVE III	WAVE V	IPL I-III	IPL I-V	IPL III-V	Zn LEVELS
1	6	20	116	14.8	1.44	3.52	5.51	2.08	4.07	1.99	1.23	3.71	5.58	2.49	4.35	1.86	131
2	7	21.5	120	15	1.46	3.49	5.4	2.03	3.94	1.91	1	3.36	5.64	2.36	4.64	2.27	106
3	6	19.5	115	14.8	1.49	3.55	5.49	2.06	4	1.94	1.56	3.4	5.75	1.84	4.19	2.35	150
4	8	24	125	15.4	1.53	3.57	5.3	2.04	3.77	1.73	1	3.78	5	2.78	4	1.22	102
5	8	25	125.4	15.9	1.5	3.5	5.48	2	3.98	1.98	1.33	3.37	4.9	2.05	3.58	1.53	120
6	7	21	119.5	14.7	1.52	3.48	5.29	1.96	3.77	1.81	1.36	3.11	5.15	1.75	3.79	2.04	149
7	11	32	139	16.6	1.47	3.46	5.28	1.99	3.88	1.82	1.51	3.3	5.28	1.79	3.76	1.98	103
8	9	27	131	15.7	1.7	3.3	5.3	1.6	3.6	2	1.48	3.41	5.08	1.94	3.6	1.66	144
9	8	23.5	124	15.3	1.49	3.48	5.4	1.99	3.91	1.92	1	4.03	5.35	3.03	4.35	1.33	111
10	10	31	136	16.8	1.5	3.51	5.39	2.01	3.89	1.79	1	3.5	5	2.5	4	1.5	119
11	6	20.5	115.5	15.4	1.46	3.47	5.29	2.01	3.83	1.82	1	3.03	5	2.03	4	1.97	125
12	8	23	124.5	14.8	1.48	3.49	5.36	2.09	3.96	1.87	1.29	3.35	5	2.06	3.71	1.65	170
13	7	22	119.2	15.5	1.5	3.55	5.31	2.05	3.81	1.76	1.59	3.59	5.37	2	3.79	1.79	67
14	6	20	114.8	15.1	1.49	3.53	5.3	2.04	3.81	1.77	1.07	3.62	5.28	2.55	4.2	1.65	128
15	10	32	136	17.3	1.5	3.51	5.33	2.01	3.83	1.82	1.59	3.16	5.16	1.57	3.58	2	75
16	11	32.5	140	16.3	1.48	3.5	5.39	2.02	3.91	1.89	1.07	3.55	5.75	2.48	4.67	2.2	60
17	8	22.4	121.8	15.14	1.7	3.47	5.21	1.77	3.51	1.74	1	3.46	5.3	2.46	4.3	1.84	88
18	8	22	123	14.6	1.46	3.49	5.3	2.03	3.84	1.81	1.64	3.04	5.81	1.4	4.17	2.77	54
19	7	21.5	119.3	15.14	1.52	3.53	5.31	2.01	3.79	1.78	1.86	3.45	5.35	1.59	3.49	1.9	133
20	9	27.5	131	16	1.49	3.54	5.3	1.95	3.81	1.76	1.65	3.58	5.1	1.93	3.45	1.53	89
21	7	20.8	119.8	14.44	1.5	3.53	5.32	2.03	3.82	1.79	1.36	3.96	5.34	2.6	3.98	1.37	121
22	6	19	115	14.4	1.44	3.51	5.34	2.07	3.9	1.84	1	3.69	5.11	2.69	4.11	1.43	117
23	7	21	120	14.6	1.47	3.45	5.29	1.98	3.82	1.84	1.49	3.25	5.9	1.76	4.41	2.65	100
24	6	19.5	115.4	14.66	1.51	4.2	6	2.69	4.49	1.8	1.87	3.06	5.08	1.19	3.2	2.01	101
25	7	22	119	15.54	1.46	3.45	5.28	1.99	3.82	1.83	1.6	3.81	5.89	2.21	4.29	2.08	114
26	8	24	124.2	15.79	1.52	3.53	5.51	2.01	3.99	1.98	0.73	3.33	5.55	2.6	4.83	2.23	97
27	9	28	132	16.09	1.49	4.12	5.8	2.63	4.31	1.68	1.29	3.34	5.01	2.05	3.73	1.67	84
28	7	20	119.7	14	1.46	3.46	5.3	2	3.84	1.84	1.64	3.21	5.41	1.58	3.78	2.2	100
29	7	19.5	118	14	1.48	3.47	5.33	1.99	3.85	1.86	1.99	3	5.99	1.01	4	2.99	61
30	6	19.5	116.2	14.4	1.52	3.56	5.6	2.04	4.08	2.04	1.05	3.5	5.46	2.45	4.41	1.96	99

MASTER CHART FOR ADHD CHILDREN

					LATENCY RT EAR (ms)						LATENCY LT EAR (ms)						µg/dl
S NO	AGE	WT	HT	BMI	WAVE I	WAVE III	WAVE V	IPL I-III	IPL I-V	IPL III-V	WAVE I	WAVE III	WAVE V	IPL I-III	IPL I-V	IPL III-V	Zn LEVELS
1	6	20	115.5	15.03	1.44	3.71	5.51	2.27	4.07	1.8	1.39	3.7	5.49	2.31	4.1	1.79	105
2	8	25	128	15.34	1.46	3.78	5.57	2.32	4.11	1.79	1.48	3.45	5.46	1.98	3.99	2.01	95
3	10	32.5	138	17.1	1.45	3.73	5.55	2.28	4.09	1.82	1.69	3.69	5.36	2	3.68	1.68	54
4	6	21	116	15.56	1.7	3.2	5.1	1.5	3.4	1.9	1.26	3.99	5.76	2.73	4.5	1.77	41
5	7	23	121	15.75	1.45	3.75	5.49	2.3	4.04	1.74	1.25	4	5.99	2.75	4.74	1.99	111
6	9	28	132	16.09	1.47	3.3	5.58	1.83	4.11	2.28	1.36	3.1	4.86	1.74	3.5	1.76	60
7	7	21	120.5	14.49	1.46	3.74	5.56	2.28	4.1	1.82	1.61	3.45	4.94	1.84	3.33	1.49	87
8	11	30.8	139	15.96	1.48	3.8	5.57	2.32	4.09	1.77	1.36	3.19	5	1.82	3.64	1.81	102
9	6	19.5	115	14.8	1.5	3.15	5.7	1.65	4.2	2.55	1.58	3.98	5.98	2.4	4.18	2	92
10	9	29	132.5	16.48	1.46	3.84	5.6	2.38	4.14	1.76	1.68	3.73	5	2.05	3.33	1.27	55
11	7	22.5	121	15.41	1.6	3.75	5.4	2.15	3.8	1.65	1.3	3.5	5.08	2.2	3.78	1.58	70
12	8	24	127	15	1.47	3.8	5.53	2.33	4.06	1.73	1.3	4.1	6.02	2.8	4.72	1.92	119
13	6	20.5	116.5	15.07	1.49	3.2	5.59	1.71	4.1	2.39	1.4	3.4	5.9	2	4.5	2.5	125
14	7	22	122	14.77	1.45	3.78	5.58	2.33	4.13	1.8	1.41	3.51	5.7	2.1	4.29	2.19	110
15	9	30	133	17	1.5	3.4	5	1.9	3.5	1.6	1.19	3.99	5.98	2.8	4.79	1.99	109
16	7	21	122	14.09	1.46	3.79	5.58	2.33	4.12	1.79	1.09	3.5	5.3	2.41	4.21	1.8	134
17	8	25.5	127	15.83	1.44	3.7	5.5	2.26	4.06	1.8	1.45	4	6	2.55	4.55	2	104
18	6	19	115	14.61	1.5	3.82	5.65	2.32	4.15	1.83	1.53	3.71	5.51	2.19	3.99	1.8	98
19	6	20.4	115	15.45	1.47	3.8	5.6	2.33	4.13	1.8	1.37	3.99	6.15	2.62	4.78	2.16	101
20	8	24	126	15.09	1.49	3.65	5	2.16	3.51	1.35	1.5	3.45	5.25	1.95	3.75	1.8	130
21	7	22.5	121	15.41	1.46	3.74	5.53	2.28	4.07	1.79	1.7	3.68	5.15	1.98	3.45	1.48	81
22	8	26	128	15.85	1.52	3.77	5.56	2.25	4.04	1.79	1.25	3.29	5.25	2.04	4	1.96	44
23	6	20	115.5	15.04	1.51	3.4	5.1	1.89	3.59	1.7	1.46	3.98	5.14	2.52	3.67	1.16	68
24	9	32	133	18.07	1.46	3.8	5.6	2.34	4.14	1.8	1.73	3.75	5.8	2.02	4.08	2.05	39
25	7	23.5	122	15.77	1.49	3.89	5.58	2.4	4.09	1.69	1.55	3.96	5.99	2.41	4.44	2.03	79
26	11	30	140	15.31	1.45	3.72	5.54	2.27	4.09	1.82	1.58	3.8	5.59	2.22	4.01	1.79	139
27	6	19.8	114	15.23	1.6	4.15	5.8	2.55	4.2	1.65	1.48	3.7	6	2.23	4.52	2.3	103
28	10	33	138	17.37	1.46	3.51	5.49	2.05	4.03	1.98	1.33	3.5	5.75	2.17	4.42	2.25	38
29	7	21.5	121	14.73	1.45	3.73	5.53	2.28	4.08	1.8	1.48	3.09	5.91	1.61	4.44	2.83	61
30	8	24.3	126.5	15.19	1.48	3.74	5.54	2.26	4.06	1.8	1.33	3.87	5.08	2.55	3.75	1.2	98

KEY TO MASTER CHART

Ht	-	Height
Wt	-	Weight
BMI	-	Body Mass Index
IPL	-	Interpeak latency
Zn	-	Zinc